Institute Report No. 435

Ninety Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats

(Volume 1 of 2)
(Part 1)

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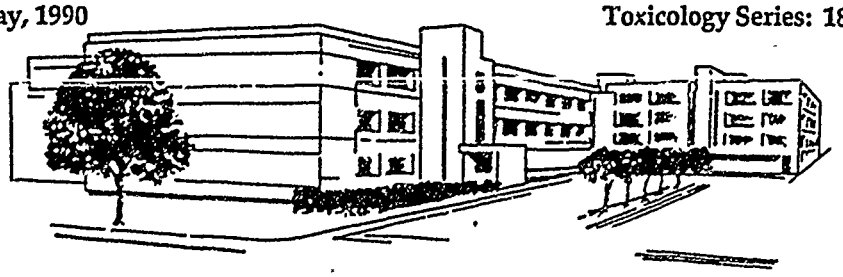
DIVISION OF TOXICOLOGY

May, 1990

Toxicology Series: 185



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Ninety Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats (Toxicology Series 185)--
Morgan *et al.*

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT APPROVED FOR PUBLIC RELEASE; DISTRIBUTION IS UNLIMITED.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Institute Report No.: 435	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Mammalian Toxicology Division of Toxicology 6b. OFFICE SYMBOL (If applicable) SGRD-ULE-T	7a. NAME OF MONITORING ORGANIZATION US Army Medical Materiel Development Activity
6c. ADDRESS (City, State, and ZIP Code) Letterman Army Institute of Research Presidio of San Francisco, CA 94129-6800	7b. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5009
8a. NAME OF FUNDING/SPONSORING ORGANIZATION US Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63002A; PROJECT NO. D995; TASK NO. BD; WORK UNIT ACCESSION NO. 176TLHO

11. TITLE (Include Security Classification)
(U) Ninety Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats

12. PERSONAL AUTHOR(S) EW Morgan, GM Zaucha, PP Waring, Y LeTellier, JB Seewald, CB Clifford, and DW Korte, Jr.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Institute	FROM 21OCT86 TO 12MAR87	May 1990	550

16. SUPPLEMENTARY NOTATION
Toxicology Series No. 185

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Subchronic Oral Toxicity, Pyridostigmine, Sprague-Dawley Rat, Acetylcholinesterase, Cholinesterase

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The 90-day subchronic oral toxicity of pyridostigmine bromide was evaluated in male and female Sprague-Dawley rats. Pyridostigmine was administered in the diet at dose levels of 0, 1, 10, 30, 60, and 90 mg/kg/day for 90 days. The addition of pyridostigmine to the diet resulted in dose-related decreases in plasma cholinesterase and erythrocyte acetylcholinesterase activity ranging from 5% to 76% and from 18% to 95%, respectively. Toxic signs associated with the decrease in cholinesterase activity included muscarinic (perianal, perioral, and periocular stains or material, diarrhea, and increased salivation) and nicotinic (hypertonia and tremors) effects. Other signs observed with increased incidence among pyridostigmine-treated animals included irritability, aggression, increased startle reflex, inactivity, jumping, hyperactivity, and chewing. The addition of pyridostigmine to the diet at the 60 and 90 mg/kg/day dose levels resulted

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED
22a. NAME OF RESPONSIBLE INDIVIDUAL DONALD G. CORBY, COL, MC	22b TELEPHONE (Include Area Code) (415) 561-3600 22c. OFFICE SYMBOL SGRD-UIZ

DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

19 (cont.) in transient reduction in food and water consumption, and correspondingly reduced weight gains for the first two weeks of the study period. Blood samples taken at necropsy for hematological and serum chemistry analyses exhibited no significant ($p \leq 0.05$) abnormalities that could be attributed to pyridostigmine dosing, and no morphologic signs of pyridostigmine-induced toxicity were detected during necropsy or subsequent microscopic examination of the tissues. These findings indicate that pyridostigmine bromide, when administered for 90 days to rats at doses that produce up to 75% inhibition of cholinesterase activity, produces little subchronic toxicity other than that attributable to cholinesterase inhibition.

ABSTRACT

The 90-day subchronic oral toxicity of pyridostigmine bromide was evaluated in male and female Sprague-Dawley rats. Pyridostigmine was administered in the diet at dose levels of 0, 1, 10, 30, 60, and 90 mg/kg/day for 90 days. The addition of pyridostigmine to the diet resulted in dose-related decreases in plasma cholinesterase and erythrocyte acetylcholinesterase activity ranging from 5% to 76% and from 18% to 95%, respectively. Toxic signs associated with the decrease in cholinesterase activity included muscarinic (perianal, perioral, and periocular stains or material, diarrhea, and increased salivation) and nicotinic (hypertonia and tremors) effects. Other signs observed with increased incidence among pyridostigmine-treated animals included irritability, aggression, increased startle reflex, inactivity, jumping, hyperactivity, and chewing. The addition of pyridostigmine to the diet at the 60 and 90 mg/kg/day dose levels resulted in transient reduction in food and water consumption, and correspondingly reduced weight gains for the first two weeks of the study period. Blood samples taken at necropsy for hematological and serum chemistry analyses exhibited no significant ($p \leq 0.05$) abnormalities that could be attributed to pyridostigmine dosing, and no morphologic signs of pyridostigmine-induced toxicity were detected during necropsy or subsequent microscopic examination of the tissues. These findings indicate that pyridostigmine bromide, when administered for 90 days to rats at doses that produce up to 75% inhibition of cholinesterase activity, produces little subchronic toxicity other than that attributable to cholinesterase inhibition.

Key Words: Subchronic Oral Toxicity, Pyridostigmine, Sprague-Dawley Rat, Acetylcholinesterase, Cholinesterase

PREFACE

TYPE REPORT: 90-Day Subchronic Oral Toxicity GLP Study Report

TESTING FACILITY:
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SPONSOR:
U.S. Army Medical Research and Development Command
U.S. Army Medical Materiel Development Activity
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PROJECT/WORK UNIT/APC: Pyridostigmine Projects/993/LLHO

GLP STUDY NUMBER: 86005

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REPORT AND DATA MANAGEMENT:
A copy of the final report, study protocol, retired SOPs, raw data, analytical, stability, and purity data of the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: Pyridostigmine bromide

INCLUSIVE STUDY DATES: 21 Oct 86 - 12 Mar 87

OBJECTIVE: The objective of this study was to determine the 90-day subchronic oral toxicity of pyridostigmine bromide in male and female Sprague-Dawley rats.

ACKNOWLEDGMENTS

SPC Theresa L. Polk, SGT Tammie Heineman, SPC Dean K. Magnuson, BS, SPC Scott L. Schwebe, Richard Katona, Gregory A. Rothhammer, Richard A. Spieler, Charlotte L. Gomez, and Obie Goodrich, Jr. provided research assistance and animal care; SPC Paul B. Simboli, BS, and SPC John R. G. Ryabik, BS, provided chemical preparation and analysis.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 86005 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

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REPLY TO ATTENTION OF

SGRD-ULX-QA

17 April 1990

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 86005

1. This is to certify that in relation to LAIR GLP Study 86005 the following inspections were made:

21 August 1986	-	Protocol Review
11 March 1987	-	Terminal Sacrifice, Females
11 March 1985	-	Blood Chemistry
18 March 1987	-	Micronucleus Test
14 April 1987	-	Diet Preparation
14 April 1987	-	Weigh Rats/Feeders, Observations
05 May 1987	-	Observations & Interim Sacrifice, Males
02 June 1987	-	Final Sacrifice, Males
02 June 1987	-	Final Observations, Weights

2. The institute report entitled "Ninety Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats," Toxicology Series 185, was audited on 12 April 1990.

Carolyn M. Lewis

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Ninety-Day Subchronic Oral Toxicity Study of Pyridostigmine Bromide in Rats -- Morgan *et al.*

INTRODUCTION

Soman, the primary nerve agent utilized by threat forces, is refractory to the standard antidotal therapy, atropine and pralidoxime (2-PAM) chloride, currently fielded by the U.S. Army. Consequently, the U.S. Army Medical Research and Development Command (USAMRDC) has proposed a treatment regimen incorporating prophylaxis with a reversible cholinesterase inhibitor and, following nerve agent exposure, antidotal therapy with an oxime and an anticholinergic agent. The rationale for this approach is that the pretreatment will protect an adequate percentage (approximately 25%) of a soldier's cholinesterase from inhibition by a nerve agent without affecting his battlefield performance. Exposure to a nerve agent would irreversibly inhibit only the remaining cholinesterase. Antidotal therapy with atropine, an anticholinergic agent, and pralidoxime, an oxime, would accomplish two goals: the oxime would reverse the inhibition induced by the reversible cholinesterase inhibitor prophylaxis, and the atropine will attenuate the excessive muscarinic response associated with cholinesterase inhibition. The immediate goal of the USAMRDC is to field a reversible cholinesterase inhibitor as the pretreatment component of a therapeutic regimen that would include antidotal therapy with 2-PAM chloride and atropine. A regimen incorporating pyridostigmine as a prophylactic agent, combined with standard atropine/2-PAM chloride therapy, has proven extremely effective in reducing mortality of Rhesus monkeys to multilethal concentrations of soman (1).

Pyridostigmine is the drug of choice for the treatment of myasthenia gravis because of its relative lack of untoward effects in comparison with other anticholinesterases (2). This relative lack of clinical toxicity was reflected in animal studies conducted for Hoffman-La Roche by Pharmacology Research, Inc. The oral LD50 for pyridostigmine in rats was calculated as 87 mg/kg and was associated with signs of cholinergic and neuromuscular toxicity (3). Pyridostigmine was also fed to rats for 21 weeks, mixed in the feed at a maximum concentration of 0.064%, without producing significant toxicity or histological changes (4). These studies suggest that the only toxicological action of pyridostigmine is on cholinesterase activity, and that death would occur acutely before morphological alterations could be observed. The carbamate, pyridostigmine bromide, was selected as a candidate reversible anticholinesterase because

it has been shown by Kluwe *et al.* (1) to be effective as the pretreatment component of a combined treatment regimen, and has been approved by the FDA for chronic treatment of myasthenia gravis.

Objective of Study

The objective of this study was to determine the 90-day subchronic toxicity of pyridostigmine bromide in male and female Sprague-Dawley rats.

MATERIALS

Test Substance

Chemical name: Pyridostigmine bromide

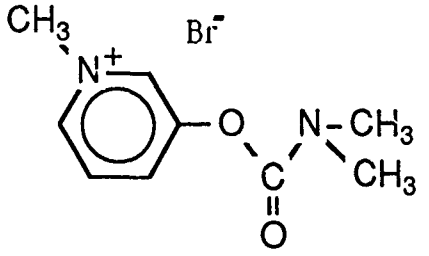
Chemical Abstracts Registry Number: 101-26-8

Lot Number: 590034

LAIR Code Number: TW71A

WRAIR Code Number: WR-250710AF

Chemical Structure:



Molecular Formula: $C_9H_{13}BrN_2O_2$

Other test substance information is presented in Appendix A.

Vehicle

The test compound was mixed into the feed (see Husbandry).

Animal Data

One hundred four male and 104 female albino Sprague-Dawley rats (Charles River Laboratories, Inc., Portage, MI) were used in this study. Tail tattoos were used to identify

each animal individually. Four males and 4 females were used for necropsy quality controls. Ten males and 10 females were used as baseline controls. The body weights on receipt (males, 21 Oct 1986; females, 25 Nov 1986) ranged from 91 g to 151 g. Additional animal data are presented in Appendix B.

Husbandry

The animals assigned to this study were housed individually in clear polycarbonate shoeboxes in drawer rack cages. Alpha-dri® (Shepherd Specialty Papers, Kalamazoo, MI), a cellulose fiber, was used as bedding. The shoeboxes and bedding were changed twice weekly. The diet, fed *ad libitum*, consisted of Certified Purina Rodent Chow® 5002 Meal Form (Ralston Purina, St. Louis, MO). Water was provided by 16-ounce water bottles with stoppers and sipper tubes. The temperature range maintained throughout this study was 20.0°C - 26.7°C with one brief decrease to 13.3°C (22 Feb 87), and a relative humidity of 24-72%. Data collected on 22 February 1987 was unaffected by the transient temperature decrease. The photoperiod was 12 hours of light daily with a 1/2-hour dawn phase-in and a 1/2-hour dusk phaseout.

METHODS

This study was performed in accordance with LAIR SOP OP-STX-74, "Subchronic Oral Toxicity Testing in Rodents," (5) as presented in Appendix C, and FDA guidelines (6). Appendix D is a complete historical listing of study events.

Group Assignment/Acclimation

The animals were acclimated for 14 or 15 days (males and females, respectively) from receipt to the onset of dosing. During the acclimation period, the animals were observed daily for signs of illness. Food and water consumption were measured during the second week of quarantine.

Male animals were assigned to treatment groups, each consisting of 15 male and 15 female study animals, and a baseline group consisting of 10 males and 10 females, using a random number generating program according to LAIR SOP OP-ISG-21 (7). The TOXSYS® Animal Allocation Program (8), a weight-biased randomization program, was used to assign the female study animals. LAIR SOP OP-ISG-21 (7) was used to select the five interim sacrifice animals for each group.

Dose Levels

The dose levels, 0, 1, 10, 30, 60, and 90 mg/kg/day, were selected on the basis of the results of a 14-day pilot study by Page and Emmerling (9) and the electron microscopy studies of Page (10).

Compound and Diet Preparation

The pyridostigmine was received as a white crystalline material, 99.6% pure (by HPLC). All diet preparations were done in accordance with LAIR SOP OP-STX-16 (11), as presented in Appendix E. Preliminary studies indicated that pyridostigmine was stable in the feed for at least 8 days. New diets were prepared each week to compensate for changes in food consumption and body weight. Separate premixes consisting of appropriate concentrations of pyridostigmine and Rodent Chow were prepared for each final dietary concentration. On the day of the diet change, after the new diet concentrations had been calculated, the appropriate amounts of premix and meal were blended together using a Patterson-Kelley Twin-Shell® Blender (Patterson-Kelley Co., Division of Harsco Corp., East Stroudsburg, PA) for at least 15 minutes. Pyridostigmine was mixed into the feed at a level that, based on the feed consumption of the previous week and the animal's weight, would provide the desired dose (mg/kg) on a daily basis. With the exception of 10% of the diet mixture samples that were within 15% of target concentrations, all diet mixes were within 10% of target concentration and were adequately homogeneous. Additional mixing data and analyses are presented in Appendix F.

Test Procedures

Food and water consumption were measured on a weekly basis. Individual feed jars were weighed at the beginning and end of each week. The feed was sifted using a 10-mesh sieve to remove bedding and feces prior to the final weighing. If there were signs of spillage in the bedding, the bedding was also sifted and the feed obtained was returned to the jar prior to weighing. Records for water bottles with obvious spillage were flagged, and the weights were omitted. Recordkeeping initiated during the final week of quarantine provided the baseline consumption data to calculate the first week's diet mixture.

Early on the day of diet change, the animals were weighed and observed, and their water bottles and feeders were weighed. These data were collected on a Beckman TOXSYS® data collection terminal. The Beckman Diet Computation

Subsystem was used for the calculations. After the new diet was mixed, the feeders and water bottles were filled, weighed, and returned to the cages.

Observations were performed twice daily throughout the 90-day test period. During the morning observations, the animals were observed undisturbed in their cages, outside of their cages, and after return to their cages. All findings were recorded. A second "walk through" observation was performed in the afternoon, and only significant observations were recorded. Body weights were recorded weekly and on the day of sacrifice.

All animals were subjected to a complete necropsy following exsanguination under sodium pentobarbital anesthesia on Day 28 (interim sacrifice) or Day 90 (terminal sacrifice). Under anesthesia, blood was collected from the right ventricle for serum chemistry, hematology, plasma cholinesterase (ChE), and erythrocyte acetylcholinesterase (AChE) activity measurements. Samples for ChE and AChE analyses were prepared in accordance with LAIR SOP OP-ACH-83 (12), Appendix G. ChE and AChE activities were determined using a Technicon Auto-Analyzer II System as described in LAIR SOP OP-ACH-83 (12), Appendix G. The following tissues were examined microscopically for all groups: diaphragm, *extensor digitorum longus* muscle, kidney, liver, lungs, soleus muscle, and all gross lesions. In addition to the tissues listed above, the following tissues were also examined microscopically for the control and 90 mg/kg/day groups: adrenal glands, aorta, femur, brain, sternum, cecum, colon, duodenum, ear, exorbital lacrimal gland, esophagus, eyes with optic nerve, Harderian gland, heart, ileum, jejunum, submandibular lymph node, mammary gland, mesenteric lymph node, mandibular/submandibular salivary gland, nose/turbinates, ovaries, pancreas, parotid salivary gland, pituitary, parathyroid, rectum, spinal cord, skin, sublingual salivary gland, skeletal muscle, sciatic nerve, spleen, stomach, thyroid, thymus, tongue, trachea, urinary bladder, uterus, male accessory sex organs, and testes.

Statistical Analysis

Data for body weights, food consumption, water consumption, serum chemistry, hematology, and cholinesterase activity were analyzed statistically with programs available on BMDP software (13). The equality of the variances of the groups was tested using the Levene's Test. If the variances were equal, the vehicle control group and the dose groups were compared by the standard one-way analysis of variance (ANOVA). Otherwise, the Welch one-way ANOVA, which is not

based on the assumption that the variances are equal, was performed. If the F-statistic was significant in either case, the Dunnett's *t* test was performed to determine whether or not the vehicle control group was significantly different from any of the dose groups. In the event that the n value for a group was greater than that of the control group, the Tukey Studentized Range Method was used instead of the Dunnett's *t* test. The preponderance of "0" values precluded any valid statistical analysis of bilirubin data. Percent inhibition of cholinesterase activities were calculated as [(mean baseline activity - normalized mean treated activity) ÷ mean baseline activity] x 100%. The normalized mean treated activity was calculated as (mean baseline activity ÷ mean control group activity) x mean treatment group activity. Statistical analyses for organ weights were done on the Xybion software program using the standard one-way ANOVA. The homogeneity of the groups was tested by the Bartlett's test. If the groups were found to be non-homogeneous, then a modified *t* test was performed instead of the Dunnett's *t* test. The incidence of microscopic lesions for each test group was compared to the control group using the Kolmogorov-Smirnov two-tailed test. The 0.05 level of significance was used for all tests.

Changes/Deviations

This study was accomplished according to the protocol and applicable amendments with the following exception: During the first week of quarantine, difficulties in adapting to the watering system resulted in slow growth for a number of male rats. The TOXSYS® Animal Allocation Program could not provide satisfactory randomization due to the increased variation in body weights. Therefore, male study animals were assigned to dose groups using a random number generating program. This deviation did not affect the outcome of this study.

Storage of Raw Data and Final Report

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

RESULTS

Food and Water Consumption

Mean daily consumption of pyridostigmine is presented in Table 1. Mean weekly food and water consumption data are

presented in Tables 2 and 3, respectively. Individual pyridostigmine, food, and water consumption data are presented in Appendices H, I, and J, respectively. Individual pyridostigmine consumption was calculated based on the mean of each animal's body weights taken at the beginning and end of each week, the individual food consumption of the animal for that week, and the pyridostigmine concentration as determined by analysis of the feed mixtures. The mean daily pyridostigmine consumption taken for the entire 13-week study period ranged from 91.5-102.8% of the target doses.

Compared to the controls, statistically significant decreases in food consumption were observed for the male study animals during weeks 1 (Groups 5 and 6) and 2 (Group 6) of the study period. Water consumption was also significantly decreased during week 1 (Group 6). However, the effect was transient, and by week 3, no significant differences from the controls were observed in the food or water consumption of the males. For the females, with the exception of a statistically significant decrease in food consumption for group 6 during week 1, food and water consumption of the treated groups were consistently increased compared to the controls throughout the study period. The increases in food consumption for the females were statistically significant at weeks 1 (Groups 3 and 4), 2 (Groups 3, 4, and 5), 8 (Group 3), and 10 (Group 3). Increases in water consumption by the females, however, were not statistically significant at any time during the study period. The increased food and water consumption exhibited by the females could not be attributed to the test compound, since the increases were already apparent during quarantine week 2, prior to the initiation of dosing.

Body Weights

Individual body weight data are presented in Appendix K. The group mean body weight data are presented in Table 4. Mean body weights for the male treatment groups were significantly less than those of the controls during weeks 1 (Groups 5 and 6) and 2 (Group 6). The decreases were transient, with no significant differences from controls being observed for the remainder of the study period. Mean body weights for the female treatment groups were consistently greater than those of the controls throughout the study period. The increases for the females were statistically significant at weeks 2 (Group 3) and 3 (Groups 3 and 5). The differences in body weights observed for the females were not attributable to the test compound, since the body weights of the controls were already lagging behind those of the treatment groups at the beginning of week 0.

TABLE 1: Daily Consumption of Pyridostigmine

Group	Week	n	Males (mg/kg/day)	n	Females (mg/kg/day)
Control	1	15	0.00*± 0.00	15	0.00 ± 0.00
	2	15	0.00 ± 0.00	15	0.00 ± 0.00
	3	15	0.00 ± 0.00	15	0.00 ± 0.00
	4	15	0.00 ± 0.00	15	0.00 ± 0.00
	5	10	0.00 ± 0.00	10	0.00 ± 0.00
	6	10	0.00 ± 0.00	10	0.00 ± 0.00
	7	10	0.00 ± 0.00	10	0.00 ± 0.00
	8	10	0.00 ± 0.00	10	0.00 ± 0.00
	9	10	0.00 ± 0.00	10	0.00 ± 0.00
	10	10	0.00 ± 0.00	10	0.00 ± 0.00
	11	10	0.00 ± 0.00	10	0.00 ± 0.00
	12	10	0.00 ± 0.00	10	0.00 ± 0.00
	13	10	0.00 ± 0.00	10	0.00 ± 0.00
1.0 mg/kg/day	1	15	1.11 ± 0.03	15	1.00 ± 0.02
	2	15	1.02 ± 0.02	15	0.88 ± 0.02
	3	15	0.87 ± 0.02	15	0.91 ± 0.02
	4	15	0.90 ± 0.02	15	0.82 ± 0.02
	5	10	0.83 ± 0.02	10	1.08 ± 0.03
	6	10	1.01 ± 0.01	10	0.81 ± 0.03
	7	10	1.00 ± 0.02	10	0.91 ± 0.03
	8	9	0.87 ± 0.02	10	0.85 ± 0.03
	9	10	0.85 ± 0.01	10	0.91 ± 0.03
	10	10	0.89 ± 0.02	9	0.88 ± 0.02
	11	10	0.87 ± 0.02	10	0.84 ± 0.02
	12	9	0.84 ± 0.02	10	1.23 ± 0.04
	13	9	1.07 ± 0.05	10	0.89 ± 0.03
10.0 mg/kg/day	1	15	9.39 ± 0.25	15	10.43 ± 0.16
	2	15	8.80 ± 0.20	14	9.35 ± 0.20
	3	14	8.49 ± 0.18	15	9.03 ± 0.19
	4	15	9.36 ± 0.20	15	9.29 ± 0.18
	5	10	7.96 ± 0.29	10	9.81 ± 0.24
	6	9	9.61 ± 0.25	10	9.53 ± 0.33
	7	10	10.28 ± 0.17	10	9.86 ± 0.25
	8	10	10.02 ± 0.17	10	9.84 ± 0.24
	9	10	9.31 ± 0.21	10	8.80 ± 0.31
	10	10	9.29 ± 0.15	10	9.59 ± 0.29
	11	10	9.47 ± 0.14	9	8.70 ± 0.45
	12	9	9.47 ± 0.19	10	12.09 ± 0.47
	13	10	10.24 ± 0.15	10	9.75 ± 0.26

* Data are presented as the mean ± the standard error.

TABLE 1 (cont.): Daily Consumption of Pyridostigmine

Group	Week	n	Males (mg/kg/day)	n	Females (mg/kg/day)
30.0 mg/kg/day	1	15	29.04*± 0.89	15	31.98 ± 0.68
	2	15	29.24 ± 0.69	15	29.93 ± 0.76
	3	15	27.21 ± 0.48	15	27.75 ± 0.43
	4	15	27.57 ± 0.60	15	28.66 ± 0.69
	5	10	25.42 ± 0.41	10	28.06 ± 0.56
	6	10	31.28 ± 0.64	10	28.40 ± 0.78
	7	10	27.93 ± 0.53	10	30.08 ± 1.29
	8	10	18.77 ± 0.43	10	29.58 ± 0.94
	9	8	27.44 ± 0.60	10	29.05 ± 0.88
	10	8	28.31 ± 0.59	10	29.91 ± 0.63
	11	10	25.66 ± 0.44	10	27.36 ± 1.09
	12	10	28.82 ± 0.58	10	35.58 ± 1.03
	13	8	30.06 ± 0.36	10	31.30 ± 1.13
60.0 mg/kg/day	1	15	54.76 ± 1.78	14	54.73 ± 1.38
	2	14	63.99 ± 1.98	14	63.60 ± 1.04
	3	15	54.27 ± 1.18	14	57.40 ± 1.29
	4	15	56.02 ± 1.18	13	55.80 ± 0.84
	5	10	56.61 ± 3.02	9	60.69 ± 0.81
	6	10	58.22 ± 1.45	9	58.28 ± 1.31
	7	10	61.02 ± 1.09	8	58.45 ± 1.36
	8	10	61.75 ± 1.35	9	59.55 ± 1.58
	9	10	59.04 ± 1.22	9	61.12 ± 0.79
	10	9	54.67 ± 1.01	9	60.21 ± 0.98
	11	10	61.29 ± 1.29	9	54.96 ± 1.40
	12	10	57.66 ± 1.08	9	69.74 ± 1.86
	13	10	63.54 ± 1.32	9	62.52 ± 1.43
90.0 mg/kg/day	1	15	67.05 ± 2.44	14	73.88 ± 2.28
	2	15	107.70 ± 2.15	15	116.89 ± 2.46
	3	15	84.36 ± 1.61	15	96.29 ± 1.80
	4	15	85.31 ± 1.80	15	84.66 ± 1.73
	5	10	77.22 ± 2.56	10	85.75 ± 2.39
	6	10	95.61 ± 2.23	10	86.15 ± 2.26
	7	10	87.27 ± 2.41	9	89.21 ± 2.46
	8	10	99.89 ± 2.20	10	84.63 ± 3.40
	9	10	81.93 ± 1.99	10	90.69 ± 1.70
	10	9	89.46 ± 2.03	9	93.81 ± 2.23
	11	10	85.00 ± 1.62	10	100.16 ± 3.73
	12	9	87.34 ± 2.22	10	106.61 ± 2.32
	13	10	129.29 ± 1.83	10	93.63 ± 2.37

* Data are presented as the mean ± the standard error.

TABLE 2: Food Consumption Summary

Group	Week	n	Males (g/week)	n	Females (g/week)
Control	1	15	171.9* ± 5.3	15	118.5 ± 3.0
	2	15	171.2 ± 4.2	14	116.2 ± 2.7
	3	15	168.2 ± 4.4	14	121.9 ± 2.8
	4	15	173.9 ± 5.0	15	118.9 ± 3.3
	5	10	172.1 ± 5.8	10	120.6 ± 3.9
	6	10	171.6 ± 6.4	10	113.9 ± 3.1
	7	10	171.0 ± 6.2	10	116.0 ± 3.2
	8	10	173.0 ± 5.2	10	116.5 ± 3.4
	9	10	178.8 ± 4.5	9	107.3 ± 4.6
	10	10	178.2 ± 5.5	10	109.4 ± 3.3
	11	9	166.7 ± 6.6	10	105.8 ± 3.3
	12	10	177.2 ± 5.7	10	113.2 ± 3.5
	13	9	178.6 ± 7.8	10	117.5 ± 3.4
1.0 mg/kg/day	1	15	164.0 ± 4.0	15	125.7 ± 3.9
	2	15	169.0 ± 2.7	15	125.7 ± 5.3
	3	15	169.5 ± 3.0	15	128.8 ± 5.0
	4	15	172.7 ± 3.4	15	119.9 ± 4.9
	5	10	161.9 ± 3.3	10	132.4 ± 6.7
	6	10	165.5 ± 2.7	10	128.9 ± 8.9
	7	10	182.3 ± 4.6	10	131.3 ± 7.7
	8	9	177.4 ± 4.6	10	124.6 ± 4.1
	9	10	172.0 ± 3.3	10	127.3 ± 6.5
	10	10	177.8 ± 5.0	9	125.8 ± 7.6
	11	10	165.9 ± 4.0	10	107.1 ± 4.5
	12	9	166.0 ± 4.3	10	117.5 ± 5.0
	13	9	176.1 ± 8.8	10	126.9 ± 5.7
10.0 mg/kg/day	1	15	164.8 ± 4.3	15	136.0@ ± 3.3
	2	15	166.7 ± 5.3	14	136.4@ ± 4.3
	3	14	167.6 ± 5.0	15	134.5 ± 4.8
	4	15	181.5 ± 4.8	15	132.1 ± 3.8
	5	10	163.1 ± 6.1	10	138.8 ± 6.0
	6	9	165.7 ± 7.7	10	126.5 ± 5.9
	7	10	171.5 ± 6.0	10	134.7 ± 5.8
	8	10	182.1 ± 7.0	10	136.3@ ± 4.9
	9	10	176.4 ± 6.8	10	127.3 ± 6.2
	10	10	178.7 ± 7.1	10	127.4@ ± 4.5
	11	10	174.4 ± 7.4	9	107.9 ± 5.8
	12	9	171.6 ± 9.2	10	129.7 ± 6.3
	13	10	176.5 ± 7.3	10	126.3 ± 5.7

* Data are presented as the mean ± the standard error.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 2 (cont.): Food Consumption Summary

Group	Week	n	Males (g/week)	n	Females (g/week)
30.0 mg/kg/day	1	15	160.7* ± 4.2	15	133.6@ ± 3.0
	2	15	171.5 ± 4.0	15	136.0@ ± 4.0
	3	15	172.1 ± 4.6	15	131.9 ± 3.9
	4	15	176.4 ± 4.6	15	127.5 ± 3.3
	5	10	169.8 ± 4.7	10	129.9 ± 2.6
	6	10	173.2 ± 5.3	10	125.8 ± 3.1
	7	10	178.3 ± 4.8	10	134.2 ± 7.4
	8	10	191.2 ± 7.0	10	128.5 ± 3.0
	9	8	172.1 ± 4.7	10	125.1 ± 3.7
	10	8	183.4 ± 7.3	10	122.4 ± 2.0
	11	10	175.8 ± 4.5	10	109.1 ± 3.4
	12	10	168.7 ± 5.7	10	122.6 ± 2.7
	13	8	169.0 ± 3.0	10	128.8 ± 4.2
60.0 mg/kg/day	1	15	140.9@ ± 7.1	14	124.1 ± 3.5
	2	14	165.9 ± 4.5	14	134.7@ ± 3.2
	3	15	168.2 ± 4.0	14	135.2 ± 4.8
	4	15	175.5 ± 4.1	13	128.2 ± 3.5
	5	10	173.4 ± 9.1	9	134.1 ± 3.0
	6	10	172.3 ± 5.2	9	128.2 ± 3.8
	7	10	169.0 ± 5.3	8	129.0 ± 5.1
	8	10	176.8 ± 5.3	9	122.4 ± 3.3
	9	10	178.8 ± 5.8	9	123.4 ± 4.2
	10	9	177.8 ± 5.9	9	117.9 ± 3.6
	11	10	172.1 ± 5.2	9	105.7 ± 4.0
	12	10	165.4 ± 4.7	9	121.0 ± 3.2
	13	10	168.0 ± 5.0	9	124.0 ± 2.5
90.0 mg/kg/day	1	15	106.8@ ± 5.8	14	97.0@ ± 3.8
	2	15	147.2@ ± 5.4	15	120.9 ± 3.7
	3	15	163.7 ± 3.9	15	129.5 ± 3.3
	4	15	176.0 ± 4.3	15	130.1 ± 4.0
	5	10	181.7 ± 6.8	10	132.0 ± 5.1
	6	10	175.7 ± 6.1	10	131.6 ± 4.0
	7	10	173.6 ± 6.7	9	135.3 ± 4.9
	8	10	189.2 ± 7.1	10	126.5 ± 5.9
	9	10	174.8 ± 6.3	10	123.6 ± 3.5
	10	9	181.9 ± 7.4	9	125.6 ± 4.5
	11	10	178.9 ± 6.5	10	113.0 ± 5.3
	12	9	170.2 ± 8.7	10	128.0 ± 4.6
	13	10	176.2 ± 5.3	10	126.0 ± 5.3

* Data are presented as the mean ± the standard error.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 3: Water Consumption Summary

Group	Week	n	Males (ml/week)	n	Females (ml/week)
Control	1	15	260.1* ± 11.1	15	197.7 ± 6.3
	2	15	264.4 ± 11.8	15	194.9 ± 6.8
	3	14	273.1 ± 13.7	15	200.7 ± 10.8
	4	15	288.3 ± 13.2	15	195.4 ± 8.7
	5	10	263.3 ± 11.6	10	214.0 ± 13.1
	6	10	256.8 ± 10.2	10	199.5 ± 14.7
	7	10	258.9 ± 12.0	10	205.4 ± 16.5
	8	10	264.6 ± 16.6	10	192.8 ± 11.2
	9	10	248.7 ± 16.2	10	204.5 ± 18.6
	10	10	263.5 ± 14.2	10	185.0 ± 11.7
	11	10	260.9 ± 13.5	10	198.1 ± 18.9
	12	10	267.3 ± 16.3	9	206.8 ± 16.6
	13	10	275.7 ± 18.9	10	212.3 ± 16.6
1.0 mg/kg/day	1	15	254.8 ± 14.9	15	212.8 ± 11.7
	2	15	256.9 ± 11.8	15	217.9 ± 12.8
	3	15	266.2 ± 13.7	13	217.1 ± 11.9
	4	15	274.3 ± 17.0	15	210.9 ± 11.2
	5	10	247.8 ± 18.6	9	225.6 ± 14.5
	6	10	241.8 ± 17.4	9	227.4 ± 13.4
	7	10	262.5 ± 15.5	10	251.3 ± 17.7
	8	10	256.2 ± 18.3	10	245.8 ± 24.0
	9	10	249.2 ± 19.9	9	224.9 ± 11.6
	10	10	253.2 ± 17.7	10	225.2 ± 16.0
	11	10	253.4 ± 17.1	9	211.3 ± 14.9
	12	10	255.1 ± 17.6	9	240.4 ± 12.9
	13	9	258.3 ± 31.3	8	258.4 ± 13.3
10.0 mg/kg/day	1	14	278.1 ± 13.2	15	224.4 ± 11.7
	2	15	283.3 ± 16.5	13	218.7 ± 12.6
	3	14	269.6 ± 12.7	14	218.5 ± 15.1
	4	15	278.5 ± 15.0	15	221.0 ± 13.3
	5	9	242.1 ± 14.8	10	239.4 ± 17.2
	6	10	273.2 ± 19.3	10	240.3 ± 17.4
	7	10	261.7 ± 18.8	10	240.7 ± 12.0
	8	10	272.6 ± 17.9	7	225.4 ± 19.9
	9	10	246.6 ± 18.9	10	221.4 ± 17.7
	10	9	295.4 ± 31.3	10	211.2 ± 14.8
	11	10	282.3 ± 25.4	10	187.1 ± 16.9
	12	10	258.0 ± 14.3	10	257.7 ± 18.1
	13	10	248.3 ± 13.6	9	219.7 ± 13.1

* Data are presented as the mean ± the standard error.

TABLE 3 (cont.): Water Consumption Summary

Group	Week	n	Males (ml/week)	n	Females (ml/week)
30.0 mg/kg/day	1	15	261.4* ± 13.0	15	225.3 ± 8.5
	2	15	265.2 ± 13.4	15	231.4 ± 12.3
	3	15	268.4 ± 13.1	15	230.0 ± 13.8
	4	15	272.5 ± 12.3	15	202.0 ± 9.3
	5	10	269.5 ± 18.7	10	216.7 ± 8.7
	6	10	274.0 ± 17.8	10	223.1 ± 11.0
	7	10	269.5 ± 16.3	10	224.3 ± 9.6
	8	10	269.6 ± 15.8	10	210.7 ± 8.3
	9	10	257.8 ± 14.8	10	225.0 ± 9.9
	10	10	266.8 ± 17.3	10	204.6 ± 9.6
	11	10	260.7 ± 16.6	10	192.9 ± 12.1
	12	10	261.2 ± 18.1	10	237.9 ± 10.8
	13	10	239.1 ± 17.5	10	224.2 ± 12.5
60.0 mg/kg/day	1	15	225.9 ± 11.5	15	214.9 ± 5.6
	2	15	242.9 ± 9.8	15	212.4 ± 5.4
	3	15	257.5 ± 11.0	15	220.2 ± 7.2
	4	15	254.3 ± 11.4	14	210.0 ± 6.3
	5	10	245.5 ± 13.7	10	223.9 ± 5.8
	6	10	243.9 ± 12.8	10	218.9 ± 9.1
	7	10	238.2 ± 12.9	10	221.4 ± 9.0
	8	10	236.1 ± 12.2	10	207.2 ± 7.6
	9	10	240.9 ± 13.5	10	214.6 ± 8.4
	10	10	237.1 ± 13.8	10	195.1 ± 8.5
	11	10	237.1 ± 12.9	10	170.4 ± 10.2
	12	10	236.3 ± 16.2	10	217.8 ± 8.6
	13	10	223.2 ± 14.5	9	210.7 ± 8.0
90.0 mg/kg/day	1	15	206.7@ ± 14.5	14	205.4 ± 12.2
	2	15	238.[illegible] ± 13.8	15	207.5 ± 11.5
	3	15	259.9 ± 14.9	15	226.3 ± 11.0
	4	15	267.2 ± 16.6	15	222.9 ± 10.3
	5	10	278.1 ± 15.6	10	241.4 ± 14.6
	6	10	278.2 ± 18.5	10	242.5 ± 13.4
	7	10	280.1 ± 20.9	10	246.9 ± 13.7
	8	10	280.5 ± 19.0	10	237.7 ± 14.8
	9	10	265.9 ± 17.0	10	230.0 ± 14.8
	10	10	275.9 ± 17.4	10	214.9 ± 12.3
	11	10	268.1 ± 17.3	9	199.0 ± 19.4
	12	10	261.5 ± 16.4	10	252.5 ± 16.0
	13	10	253.1 ± 17.0	10	240.0 ± 14.6

* Data are presented as the mean ± the standard error.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 4: Body Weight Summary

Group	Week	Males n	Males (g)	Females n	Females (g)
Control	1	15	287* ± 8	15	217 ± 4
	2	15	326 ± 9	15	232 ± 4
	3	15	358 ± 9	15	241 ± 5
	4	15	388 ± 9	15	252 ± 6
	5	10	413 ±14	10	264 ± 9
	6	10	438 ±16	10	269 ± 9
	7	10	457 ±16	10	274 ± 8
	8	10	476 ±16	10	281 ± 9
	9	10	488 ±16	10	282 ±10
	10	10	506 ±16	10	289 ±10
	11	10	520 ±16	10	287 ± 9
	12	10	532 ±17	10	298 ± 9
	13	10	544 ±17	10	302 ±10
1.0 mg/kg/day	1	15	287 ± 6	15	221 ± 5
	2	15	329 ± 5	15	240 ± 7
	3	15	362 ± 5	15	255 ± 8
	4	15	393 ± 5	15	264 ± 7
	5	10	414 ± 6	10	278 ± 9
	6	10	439 ± 5	10	289 ±13
	7	10	461 ± 6	10	298 ±13
	8	10	477 ± 7	10	303 ±12
	9	10	492 ± 6	10	315 ±13
	10	10	508 ± 7	10	321 ±15
	11	10	519 ± 7	10	318 ±15
	12	10	528 ± 8	10	330 ±15
	13	10	522 ±13	10	335 ±16
10.0 mg/kg/day	1	15	278 ± 8	15	229 ± 4
	2	15	321 ± 9	15	252@ ± 6
	3	15	358 ± 9	15	265@ ± 7
	4	15	390 ±10	15	274 ± 6
	5	10	409 ±12	10	294 ±10
	6	10	432 ±13	10	298 ±12
	7	10	453 ±13	10	305 ±13
	8	10	473 ±14	10	314 ±12
	9	10	487 ±14	10	324 ±13
	10	10	505 ±16	10	332 ±14
	11	10	518 ±17	10	324 ±14
	12	10	528 ±18	10	341 ±14
	13	10	545 ±19	10	342 ±15

* Data are presented as the mean ± the standard error.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 4 (cont.): Body Weight Summary

Group	Week	Males n	Males (g)		Females n	Females (g)	
30.0 mg/kg/day	1	15	281*	±10	15	221	± 4
	2	15	325	±10	15	241	± 5
	3	15	362	±11	15	259	± 6
	4	15	393	±11	15	266	± 6
	5	10	416	±15	10	273	± 6
	6	10	434	±16	10	280	± 6
	7	10	454	±16	10	288	± 7
	8	10	479	±16	10	294	± 6
	9	10	494	±17	10	299	± 6
	10	10	515	±19	10	305	± 7
	11	10	524	±18	10	299	± 6
	12	10	538	±21	10	311	± 7
	13	10	552	±19	10	315	± 7
60.0 mg/kg/day	1	15	251@	±11	15	227	± 4
	2	15	300	±10	15	248	± 5
	3	15	339	±10	15	268@	± 6
	4	15	369	±10	15	276	± 6
	5	10	403	±15	10	292	± 7
	6	10	426	±15	10	297	± 7
	7	10	446	±15	10	311	± 8
	8	10	469	±15	10	310	± 7
	9	10	485	±15	10	320	± 8
	10	10	503	±16	10	321	± 8
	11	10	517	±16	10	318	± 9
	12	10	529	±16	10	329	± 8
	13	10	539	±16	10	329	± 8
90.0 mg/kg/day	1	15	243@	± 9	15	207	± 4
	2	15	285@	± 9	15	229	± 5
	3	15	328	± 9	15	248	± 5
	4	15	360	± 8	15	262	± 6
	5	10	399	±11	10	277	± 8
	6	10	425	±11	10	286	± 7
	7	10	442	±12	10	300	± 8
	8	10	464	±13	10	305	± 8
	9	10	481	±12	10	310	± 9
	10	10	500	±14	10	314	± 9
	11	10	515	±14	10	312	± 9
	12	10	527	±15	10	326	±11
	13	10	540	±16	10	328	±10

* Data are presented as the mean ± the standard error.
@ Significant difference from controls at $p \leq 0.05$.

Clinical Observations

A summary of clinical observations is presented in Table 5. Individual animal histories are presented in Appendix L. The clinical signs observed were grouped into reflexive, behavioral, respiratory, skin/fur, ocular, gastrointestinal, and general categories. No deaths occurred during the study.

The most frequently observed signs were of the behavioral category (121 of 150 treated animals). These signs included irritability, aggression, inactivity, jumping, hypertonia, hyperactivity, chewing, and tremors. All behavioral signs were observed with slightly increased incidence in the treatment groups as compared to the controls. Among pyridostigmine-treated animals, irritability and aggression were the most prominent behavioral signs, while inactivity, jumping, hypertonia, hyperactivity, chewing, and tremors occurred sporadically.

The only reflexive sign observed, increased startle reflex (104 of 150), appeared to be dose-related, occurring most frequently in the high-dose groups.

Respiratory signs characterized by stains or material around the nose (85 of 150) were observed with relatively equal distribution among the treated and control groups.

Abnormalities of the skin/fur occurred with increased incidence in the pyridostigmine-treated animals (66 of 150). Rough coat was observed most frequently in the males, while stains or material on various parts of the body were observed most frequently in the females. Other skin/fur signs were observed with relatively equal distribution among treated and control groups.

Ocular signs observed (19 of 150) included stain or material around the eyes, conjunctivitis, corneal erosion, corneal opacity, and chromodacryorrhea. Although female animals treated with pyridostigmine exhibited an increased incidence of conjunctivitis and stains or material around the eyes, males were unaffected compared to the controls. Corneal erosion, corneal opacity, and chromodacryorrhea occurred in no more than one animal of each affected group.

Gastrointestinal signs observed (13 of 150) included perianal stain/feces, stains around the mouth, diarrhea, and increased salivation. Although relatively sporadic, the incidence of gastrointestinal signs appeared to be dose-related. None of the control or low-dose animals exhibited any gastrointestinal signs.

The general signs, emaciation and dehydration, occurred in isolated cases unrelated to treatment group.

Serum Chemistry

Individual serum chemistry values are presented in Appendix M. A summary of serum chemistry data is presented in Table 6. Although statistically significant variations from control values were observed for several serum chemistry measurements (blood urea nitrogen, phosphorus, sodium, chloride, lactate dehydrogenase, total protein, albumin, and iron), the affected parameters generally remained within clinically acceptable limits and no treatment-related trends were observed. Alterations from control values were inconsistent among treatment groups or sexes, and appeared to be relatively random incidents with little if any clinical significance.

Hematology

Individual hematology data are presented in Appendix N. Group mean summary data are presented in Table 7. No clinically significant variations or treatment-related trends in hematology measurements were observed during the study period. Statistically significant differences from control values were observed in the mean corpuscular hemoglobin concentration for males and females, but the actual variations from control values were very slight and had no clinical relevance. Statistically significant variations from control values were also observed for hematocrit and white blood cell count, but they were isolated incidents also lacking clinical significance.

Cholinesterase Activity

Individual plasma cholinesterase (ChE) and erythrocyte acetylcholinesterase (AChE) activities are presented in Appendix M. Group mean ChE and AChE data are presented in Table 6. Percent inhibition calculations are presented in Table 8. In general, ChE and AChE activity levels exhibited dose-related decreases compared to control levels for both sexes. Exceptions occurred in the low-dose groups at Day 28, when the ChE levels for Group 2 males and Group 2 and 3 females, and the AChE levels for Group 2 females increased compared to controls. An exception to the dose-response also occurred at Day 28 when the mean AChE for Group 6 males, although decreased compared to control values, did not follow the typical dose-response relationship. The decreases in

TABLE 5: Clinical Observations Summary*

Group (mg/kg/day) Observation	Control	1.0	10.0	30.0	60.0	90.0
			Males			
NORMAL THROUGHOUT	3	1	3	3	-	-
BEHAVIORAL	11	10	12	12	13	14
IRRITABLE	11	10	11	12	13	13
AGGRESSIVE	1	1	3	6	2	2
HYPERACTIVE	-	-	-	-	1	-
JUMPING	-	-	-	-	-	5
TREMORS	-	-	-	-	-	1
INACTIVE	-	-	1	1	-	3
REFLEXIVE	2	3	4	9	14	13
INCR. STARTLE REFLEX	2	3	4	9	14	13
RESPIRATORY	6	8	9	7	9	9
STAIN/MATERIAL NOSE	6	8	9	7	9	9
SKIN/FUR	2	4	3	3	4	9
ROUGH COAT	1	2	1	1	3	7
ALOPECIA	-	3	1	-	-	3
STAIN/MATERIAL LEG, BACK, NECK, HEAD, EAR, ABDOMEN	1	2	2	3	1	1
OCULAR	1	-	-	1	-	-
STAIN/MATERIAL EYE	-	-	-	1	-	-
CHROMODACRYORRHEA	1	-	-	-	-	-
GASTROINTESTINAL	-	-	1	-	3	4
PERIANAL STAIN/FECES	-	-	1	-	3	2
STAIN MOUTH	-	-	-	-	-	2
DIARRHEA	-	-	-	-	1	-
GENERAL	-	-	-	-	-	2
DEHYDRATED	-	-	-	-	-	2
EMACIATED	-	-	-	-	-	1

* Data presented as number of animals exhibiting the sign with 15 animals per group.

TABLE 5 (cont.): Clinical Observations Summary*

Group (mg/kg/day) Observation	Control	1.0	10.0	30.0	60.0	90.0
			Females			
NORMAL THROUGHOUT	3	-	1	-	-	-
BEHAVIORAL	8	12	13	10	13	12
IRRITABLE	8	12	13	10	13	12
AGGRESSIVE	1	-	2	1	4	3
CHEWING	-	2	1	-	-	-
HYPERACTIVE	-	-	-	1	-	1
HYPERTONIA	-	-	-	-	1	3
REFLEXIVE	8	7	13	12	14	15
INCR. STARTLE REFLEX	8	7	13	12	14	15
RESPIRATORY	8	10	8	8	9	8
STAIN/MATERIAL NOSE	8	10	8	8	9	8
SKIN/FUR	6	8	10	9	5	11
ROUGH COAT	1	1	3	4	1	1
ALOPECIA	5	6	6	3	2	5
STAIN/MATERIAL LEG, BACK, NECK, HEAD, EAR, ABDOMEN	2	4	4	5	5	8
SCAB LEG, BACK, NECK	2	1	2	2	-	1
HAIR CLUMPED	1	-	-	-	-	-
OCULAR	-	2	1	6	4	5
STAIN/MATERIAL EYE	-	1	-	3	4	2
CONJUNCTIVITIS	-	-	1	2	-	4
CORNEAL EROSION	-	1	-	1	-	-
CORNEAL OPACITY	-	-	-	1	-	-
GASTROINTESTINAL	-	-	1	1	-	3
INCR. SALIVATION	-	-	-	-	-	1
STAIN MOUTH	-	-	1	1	-	1
DIARRHEA	-	-	-	-	-	1
GENERAL	1	-	1	-	-	1
DEHYDRATED	1	-	1	-	-	1
EMACIATED	-	1	-	-	-	-

* Data presented as number of animals exhibiting the sign with 15 animals per group.

TABLE 6: Serum Chemistry Summary*

		Males					
Group	Baseline	Control		1.0 mg/kg/day		10.0 mg/kg/day	
Day	0	28	90	28	90	28	90
n	9	5	10	5	10	5	10
ACHE U/ml	1.4333 ±0.1967	2.0840 0.9129	1.6468 0.2225	1.5448 0.4673	1.1484@ 0.2470	1.4418 0.5141	0.9666@ 0.1958
CHE U/ml	0.3367 ±0.0810	0.2876 0.0215	0.2830 0.0728	0.2986 0.0639	0.2412 0.0760	0.1540@ 0.0364	0.1414@ 0.0253
ALT U/l	56.58 ±9.61	50.54 16.89	99.21 98.34	49.74 9.41	84.89 96.38	54.80 24.40	50.33 17.65
AST U/l	138.67 ±64.79	129.14 69.52	164.42 108.24	94.80 20.29	243.43 445.10	129.24 71.65	126.64 26.84
ALK U/l	254.66 ±55.92	196.18 59.25	162.97 53.53	198.52 44.24	187.09 68.20	232.96 48.21	152.48 56.51
LDH U/l	601.80 ±305.44	520.26 346.49	939.26 307.70	459.14 193.19	499.41 269.55	927.34 1034.26	1158.02 338.87
CK U/l	853.17 ±386.24	1457.80 1323.84	630.03 181.82	702.44 408.53	398.70 163.79	676.76 95.21	1122.97 568.54
BILI mg/dl	0.000 ±0.000	0.000 0.000	0.005 0.016	0.000 0.000	0.007 0.019	0.000 0.000	0.020 0.037
CHOL mg/dl	58.26 ±10.97	64.02 20.29	59.13 14.24	70.72 15.95	63.10 16.55	68.04 24.12	68.44 11.91
TRIG mg/dl	91.99 ±33.65	182.48 135.29	195.06 60.14	119.62 47.43	173.70 74.54	141.54 56.78	185.52 65.58
URIC mg/dl	2.44 ±0.50	3.26 1.99	1.69 0.70	2.40 0.94	1.74 0.68	2.94 1.74	1.83 0.80
TP g/dl	5.14 ±0.25	5.86 0.72	6.20 0.45	5.62 0.36	6.11 0.61	5.68 0.37	6.51 0.47

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 6 (cont.): Serum Chemistry Summary*

	Males					
Group	30.0 mg/kg/day		60.0 mg/kg/day		90.0 mg/kg/day	
Day	28	90	28	90	28	90
n	5	10	5	10	5	10
ACHE	1.3750	0.5446†@	0.6940	0.2881@	1.4826	0.1865@
U/ml	±0.5331	0.1148	0.8335	0.3196	0.2910	0.1490
CHE	0.0924@	0.1103†@	0.0924@	0.0925@	0.0808@	0.0672@
U/ml	±0.0174	0.0513	0.0357	0.0269	0.0108	0.0122
ALT	42.22	48.75	49.86	59.58	40.20	44.44
U/l	±6.58	15.44	7.21	43.82	2.30	10.22
AST	105.36	120.09	109.60	169.49	87.96	100.33
U/l	±22.06	53.86	31.08	177.35	6.24	25.72
ALK	188.06	130.85	206.92	107.34	212.70	138.34
U/l	±39.86	55.79	76.14	40.22	42.74	30.05
LDH	760.50	676.73	526.42	673.40	473.62	572.42
U/l	±491.49	469.99	200.22	559.54	112.02	369.55
CK	909.84	1324.15	955.66	1187.56	561.34	521.54
U/l	±247.66	1990.96	644.23	2031.49	74.45	209.48
BILI	0.000	0.014	0.000	0.009	0.000	0.000
mg/dl	±0.000	0.030	0.000	0.019	0.000	0.000
CHOL	70.12	65.01	55.36	55.82	46.50	60.15
mg/dl	±13.12	12.86	13.33	9.13	9.83	11.89
TRIG	123.22	224.65	122.65$	221.63†	94.30	243.19
mg/dl	±40.66	89.12	36.57	106.45	20.77	116.22
URIC	1.44	1.79	2.40	2.28	3.36	1.81
mg/dl	±0.42	0.62	1.16	2.29	1.04	0.77
TP	5.58	6.23	5.88	6.31	5.56	5.93
g/dl	±0.38	0.47	0.49	0.43	0.32	0.38

* Data are presented as the mean ± the standard deviation.
† The number of animals per group, n, equals 9.
@ Significant difference from controls at $p \leq 0.05$.
$ The number of animals per group, n, equals 4.

TABLE 6 (cont.): Serum Chemistry Summary*

		Males					
Group	Baseline	Control		1.0 mg/kg/day		10.0 mg/kg/day	
Day	0	28	90	28	90	28	90
n	9	5	10	5	10	5	10
ALB	2.776	2.892	3.169	2.812	3.262	2.930	3.416
g/dl	±0.208	0.420	0.210	0.258	0.228	0.322	0.264
GLU	237.83	285.42	232.71	277.44	221.64	270.56	236.15
mg/dl	±29.79	72.98	15.59	38.99	66.57	51.65	30.98
BUN	15.84	19.36	23.03	20.20	23.22	19.72	20.69
mg/dl	±2.53	2.86	2.99	2.76	4.19	1.42	2.88
CR	0.451	0.652	0.621	0.622	0.635	0.608	0.635
mg/dl	±0.079	0.137	0.087	0.076	0.066	0.209	0.103
CAL	10.98	11.44	10.33	10.94	10.69	10.86	11.31
mg/dl	±0.56	1.35	0.76	0.41	0.75	0.93	0.79
PHOS	9.833	9.580	6.670	9.140	6.918	9.700	7.108
mg/dl	±0.870	1.446	0.963	0.984	1.160	1.037	1.452
NA	146.3	142.4	140.9	144.6	142.3	145.4	140.1
Meq/l	±3.0	2.2	3.9	2.4	5.0	3.2	5.9
CL	101.8	99.4	101.4	104.4	102.1	102.0	104.1
Meq/l	±2.2	2.1	4.1	4.5	4.7	1.6	5.1
K	6.50	6.52	5.85	6.56	5.85	7.80	5.69
Meq/l	±0.43	1.22	0.69	1.46	0.53	1.25	0.60
IRON	287.3	191.4	171.5	219.2	189.4	165.2	158.8
µg/dl	±106.6	44.3	20.5	46.7	62.1	42.2	38.7
MAG	2.723	2.956	2.461	2.578	2.499	2.758	2.672
mg/dl	±0.131	0.388	0.202	0.340	0.226	0.413	0.340

* Data are presented as the mean ± the standard deviation.

TABLE 6 (cont.): Serum Chemistry Summary*

Group	Males					
	30.0 mg/kg/day		60.0 mg/kg/day		90.0 mg/kg/day	
Day	28	90	28	90	28	90
n	5	10	5	10	5	10
ALB	2.894	3.427	2.996	3.287	2.948	3.273
g/dl	±0.099	0.361	0.243	0.217	0.123	0.207
GLU	252.42	241.39	247.62	269.23	249.18	232.74
mg/dl	±18.73	15.11	60.92	63.43	20.08	41.09
BUN	18.64	20.45	19.04	17.27@	16.04	19.15@
mg/dl	±3.11	2.26	2.67	1.96	2.58	2.67
CR	0.680	0.630	0.680	0.635	0.608	0.630
mg/dl	±0.070	0.118	0.064	0.110	0.077	0.075
CAL	10.46	10.97	10.68	11.26	11.12	10.75
mg/dl	±0.80	0.81	0.54	0.99	0.58	0.62
PHOS	8.420	7.249	9.700	8.882@	9.600	7.368
mg/dl	±0.835	0.746	0.771	2.839	0.495	0.790
NA	144.2	142.3	147.4	142.1†	141.8	142.6
Meq/l	±3.1	3.9	3.3	3.9	2.9	3.4
CL	101.4	104.6	101.8	105.9	101.2	107.2@
Meq/l	±1.1	2.6	2.8	4.4	1.6	4.8
K	5.74	5.75	6.62	5.69†	7.12	5.65
Meq/l	±0.75	0.59	0.86	0.53	1.26	0.38
IRON	177.4	152.5	163.6	144.6	179.6	178.6
µg/dl	±40.6	24.3	32.6	29.6	42.1	87.9
MAG	2.446	2.523	2.624	2.471	2.854	2.312
mg/dl	±0.190	0.170	0.319	0.437	0.152	0.234

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.
† The number of animals per group, n, equals 9.

TABLE 6 (cont.): Serum Chemistry Summary*

		Females					
Group	Baseline	Control		1.0 mg/kg/day		10.0 mg/kg/day	
Day	0	28	90	28	90	28	90
n	10	5	10	5	10	5	10
ACHE U/ml	1.5720 ±0.6128	1.4754 0.1069	1.0236 0.3541	1.5914 0.2158	0.2704@ 0.5021	1.2026 0.1932	0.2223@ 0.3528
CHE U/ml	0.5999 ±0.0900	0.4522 0.0775	1.0783 0.4123	0.8176@ 0.2760	0.9416 0.2342	0.5266 0.1111	0.7869 0.2779
ALT U/l	43.75 ±7.35	36.70 3.45	59.42 30.60	48.22 11.69	47.93 16.51	42.96 6.46	45.30 18.81
AST U/l	170.54 ±79.25	98.14 19.08	157.38 77.56	191.44 113.57	128.13 40.14	125.36 39.84	119.08 46.78
ALK U/l	208.42 ±28.55	165.10 40.89	98.40 32.15	160.28 57.30	88.75 30.84	119.36 33.33	99.50 35.79
LDH U/l	685.47 ±392.17	330.24 129.57	710.49 335.85	952.16@ 336.12	605.81 260.09	552.08 84.02	543.16 354.95
CK U/l	2911.29 ±3451.05	467.46 222.72	700.63 262.55	2419.98 3075.92	945.70 1039.49	685.90 234.30	770.89 621.10
BILI mg/dl	0.000 ±0.000	0.000 0.000	0.001 0.003	0.000 0.000	0.005 0.008	0.000 0.000	0.000 0.000
CHOL mg/dl	60.76 ±7.75	66.16 13.69	75.00 20.78	70.80 12.79	60.82 8.65	73.14 8.99	61.74 12.43
TRIG mg/dl	75.73 ±28.56	60.72 13.91	124.51 55.34	73.45$ 51.26	138.80 76.52	104.92 27.53	98.17 36.85
URIC mg/dl	2.80 ±0.70	1.68 0.31	2.44 0.88	2.94 1.84	2.19 0.92	2.26 0.58	1.68 0.61
TP g/dl	5.17 ±0.32	5.66 0.30	6.84 0.61	6.18$ 0.32	6.66 0.57	6.10 0.26	6.11 0.56

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.
$ The number of animals per group, n, equals 4.

TABLE 6 (cont.): Serum Chemistry Summary*

	Females					
Group	30.0 mg/kg/day		60.0 mg/kg/day		90.0 mg/kg/day	
Day	28	90	28	90	28	90
n	5	10	5	9	5	10
ACHE U/ml	0.9096@ ±0.1797	0.1774@ 0.2316	0.7480@ 0.1269	0.1490@ 0.1630	0.5814@ 0.1386	0.0468@ 0.1233
CHE U/ml	0.4300 ±0.1712	0.5288@ 0.2609	0.2960 0.1165	0.4628@ 0.2543	0.2854 0.0899	0.3799@ 0.1657
ALT U/l	41.04 ±8.32	52.61 25.28	35.38 3.47	55.28 29.30	39.76 5.99	57.70 21.23
AST U/l	135.10 ±85.52	145.46 82.07	116.38 57.98	140.02 45.13	130.08 55.15	161.32 66.75
ALK U/l	165.88 ±66.57	130.79 36.62	115.28 33.34	94.72 20.47	157.60 41.09	86.09 31.68
LDH U/l	433.24 ±322.86	647.88 267.38	595.04 298.47	548.91 261.01	678.74 195.96	562.80 282.48
CK U/l	454.54 ±116.24	604.92 234.06	675.46 377.44	492.53 149.01	723.36 370.65	896.40 645.56
BILI mg/dl	0.000 ±0.000	0.000 0.000	0.000 0.000	0.000 0.000	0.000 0.000	0.000 0.000
CHOL mg/dl	81.50 ±6.88	53.50 19.76	68.76 14.80	63.46 14.16	72.34 6.34	63.70 12.66
TRIG mg/dl	82.88$ ±41.49	121.36 63.56	58.86 5.92	91.29 40.74	59.26 17.56	90.97† 46.69
URIC mg/dl	2.06 ±0.46	2.24 0.56	2.16 0.44	2.07 0.75	2.64 1.29	2.17 1.07
TP g/dl	6.26@ ±0.48	6.52 0.47	6.04 0.21	6.50 0.30	5.96 0.45	6.46 0.66

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.
$ The number of animals per group, n, equals 4.
† The number of animals per group, n, equals 9.

TABLE 6 (cont.): Serum Chemistry Summary*

		Females					
Group	Baseline	Control		1.0 mg/kg/day		10.0 mg/kg/day	
Day	0	28	90	28	90	28	90
n	10	5	10	5	10	5	10
ALB	2.983	3.124	4.021	3.388$	3.866	3.300	3.520@
g/dl	±0.273	0.398	0.392	0.178	0.262	0.193	0.595
GLU	264.19	223.96	223.20	258.66	233.95	227.64	210.14
mg/dl	±26.55	24.08	34.07	17.04	32.58	31.65	43.98
BUN	16.50	17.76	18.17	15.46	19.11	21.18	21.31
mg/dl	±3.11	1.09	3.52	6.46	3.18	6.52	1.74
CR	0.433	0.574	0.729	0.488	0.669	0.632	0.595
mg/dl	±0.147	0.065	0.091	0.126	0.102	0.071	0.081
CAL	11.20	10.42	10.93	10.70	10.69	10.78	10.25
mg/dl	±0.52	0.58	0.45	0.76	0.69	0.70	0.55
PHOS	9.840	5.440	5.471	6.950$	6.314	5.860	5.803
mg/dl	±1.338	0.966	1.670	0.473	1.953	0.932	1.307
NA	149.6	148.4	144.0	149.3$	149.7@	149.2	142.5
Meq/l	±3.0	3.5	2.7	4.1	4.1	4.8	2.1
CL	103.5	102.0	105.5	102.3$	102.5	101.0	104.0
Meq/l	±1.1	2.1	3.0	2.9	3.1	4.7	2.4
K	6.78	5.80	5.70	6.28$	6.09	6.42	5.48
Meq/l	±0.89	0.46	0.78	0.84	1.03	0.47	0.74
IRON	299.6	333.8	347.0	232.3$	295.7	255.4	280.5
µg/dl	±68.0	54.1	69.2	70.0	73.8	35.2	69.0
MAG	2.776	2.520	2.651	3.002	2.470	2.858	2.308
mg/dl	±0.198	0.237	0.270	0.562	0.224	0.235	0.349

* Data are presented as the mean ± the standard deviation.
$ The number of animals per group, n, equals 4.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 6 (cont.): Serum Chemistry Summary*

	Females					
Group	30.0 mg/kg/day		60.0 mg/kg/day		90.0 mg/kg/day	
Day	28	90	28	90	28	90
n	5	10	5	9	5	10
ALB	3.402	3.353@	3.296	3.517@	3.246	3.922
g/dl	±0.290	0.347	0.101	0.220	0.322	0.381
GLU	215.14	218.08	222.78	218.69	229.70	230.56
mg/dl	±10.79	34.22	38.04	29.97	28.67	18.72
BUN	19.36	17.73	18.18	16.32	15.16	19.11
mg/dl	±1.43	2.36	3.19	2.86	2.73	3.59
CR	0.600	0.644	0.652	0.677	0.590	0.650
mg/dl	±0.123	0.075	0.084	0.114	0.044	0.096
CAL	10.96	10.67	10.34	10.87	10.60	10.75
mg/dl	±0.43	0.59	0.53	0.47	0.80	0.79
PHOS	8.000$@	5.422	7.860@	5.026	9.140@	6.137
mg/dl	±1.128	1.566	1.104	0.974	1.069	1.289
NA	150.2	141.1	147.0	141.2	147.8	142.7
Meq/l	±5.8	1.6	3.9	2.0	5.6	6.9
CL	102.6	105.6	103.0	108.3	105.6	110.4@
Meq/l	±3.7	2.5	2.8	2.6	4.2	4.9
K	5.88	5.63	5.84	5.00	6.28	5.66
Meq/l	±0.55	1.07	0.93	0.72	0.78	0.90
IRON	249.8	328.7	222.2	289.9	263.4	268.6@
µg/dl	±23.3	23.6	52.1	58.0	91.4	44.7
MAG	2.638	2.611	2.728	2.404	2.732	2.544
mg/dl	±0.142	0.210	0.249	0.263	0.328	0.289

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.
$ The number of animals per group, n, equals 4.

TABLE 7: Hematology Summary*

		Males					
Group	Baseline	Control		1.0 mg/kg/day		10.0 mg/kg/day	
Day	0	28	90	28	90	28	90
n	10	5	10	5	10	5	10
RBC	5.925	7.270	7.801	7.338	7.673	6.724	7.202
$x10^6/\mu l$	±0.672	0.304	0.540	0.402	0.470	1.192	0.435
HGB	13.15	15.40	15.21	15.32	15.05	14.48	14.56
g/dl	±1.61	0.41	0.67	0.71	0.61	2.23	0.41
HCT	37.04	43.06	42.04	42.94	41.48	39.88	39.07@
%	±4.26	1.45	1.70	2.28	2.11	7.07	0.82
MCV	61.0	59.0	53.3	58.4	54.1	59.4	53.3
fl	±1.3	1.2	2.2	1.9	1.8	1.8	1.1
MCH	22.27	21.06	19.22	20.80	19.58	21.54	19.83
pg	±0.74	0.30	0.66	0.58	0.65	0.78	0.49
MCHC	35.43	33.28	36.00	35.48	36.11	36.22	37.01@
g/dl	±0.66	5.04	0.53	0.43	0.56	1.18	0.47
RET	0.40	0.36	0.78	0.20	0.52	0.28	1.36
%	±0.30	0.22	0.38	0.24	0.33	0.23	1.04
PLT	795.7	587.6	843.0	728.8	810.4	584.4	752.1
$x10^3/\mu l$	±144.6	77.9	144.6	286.2	274.3	151.3	107.1
WBC	5.10	9.18	6.00	6.48	6.91	7.02	6.94
$x10^3/\mu l$	±1.39	3.23	0.89	2.90	2.56	2.71	2.46
SEG	17.0	17.8	13.6	12.6	16.1	14.2	13.7
%	±8.4	13.7	4.8	6.7	10.2	1.3	5.8
BAN	0.0	0.2	0.0	0.0	0.0	0.2	0.0
%	±0.0	0.4	0.0	0.0	0.0	0.4	0.0
EOS	0.2	0.2	0.4	0.4	0.3	0.4	0.8
%	±0.4	0.4	0.5	0.5	0.5	0.5	0.8
LYM	82.5	81.8	86.0	86.6	83.6	85.2	85.5
%	±8.0	13.5	4.8	6.7	10.0	1.5	5.9
MON	0.3	0.0	0.0	0.0	0.0	0.0	0.0
%	±0.5	0.0	0.0	0.0	0.0	0.0	0.0

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 7 (cont.): Hematology Summary*

	Males					
Group	30.0 mg/kg/day		60.0 mg/kg/day		90.0 mg/kg/day	
Day	28	90	28	90	28	90
n	5	9	5	10	5	9
RBC	7.150	7.608	6.886	7.541	7.062	7.486
$x10^6/\mu l$	±0.246	0.256	0.527	0.584	0.607	0.418
HGB	15.10	15.00	15.18	14.62	15.10	15.06
g/dl	±0.58	0.48	0.61	0.73	0.42	0.78
HCT	41.56	40.64	41.26	39.73@	41.74	40.62
%	±2.06	1.31	1.97	2.29	1.22	2.22
MCV	58.2	53.4	58.2	52.7	57.2	53.6
fl	±3.1	0.7	1.3	2.4	1.5	1.1
MCH	20.98	19.69	21.32	19.38	20.70	19.74
pg	±0.91	0.39	0.57	0.88	0.59	0.49
MCHC	36.12	36.72@	36.52	36.63@	36.00	36.83@
g/dl	±0.55	0.42	0.36	0.67	0.00	0.47
RET	0.20	0.53	0.32	0.67	0.40	0.80
%	±0.35	0.60	0.46	0.71	0.37	0.45
PLT	801.2	861.3	642.0	971.6	604.3	866.9
$x10^3/\mu l$	±127.9	190.7	110.5	75.8	164.4	172.0
WBC	7.08	6.48	5.78	7.35	5.66	7.10
$x10^3/\mu l$	±2.91	1.33	3.09	1.30	1.38	1.42
SEG	9.6	10.2	21.8	13.7	15.0	13.0
%	±8.8	4.2	16.5	6.7	7.4	7.7
BAN	0.0	0.0	0.0	0.0	0.0	0.0
%	±0.0	0.0	0.0	0.0	0.0	0.0
EOS	0.4	0.2	0.6	0.3	0.0	0.2
%	±0.5	0.4	0.5	0.5	0.0	0.4
LYM	90.0	89.6	77.6	85.9	85.0	86.8
%	±9.2	4.1	16.3	6.6	7.4	7.6
MON	0.0	0.0	0.0	0.1	0.0	0.0
%	±0.0	0.0	0.0	0.3	0.0	0.0

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 7 (cont.): Hematology Summary*

		Females					
Group	Baseline	Control		1.0 mg/kg/day		10.0 mg/kg/day	
Day	0	28	90	28	90	28	90
n	10	5	10	5	9	5	8
RBC	6.155	6.174	7.241	6.862	7.233	6.726	7.314
$x10^6/\mu l$	±0.286	1.156	0.693	0.288	0.467	0.155	0.213
HGB	14.03	13.60	15.49	14.98	15.04	14.58	15.11
g/dl	±0.72	2.58	0.57	0.70	0.79	0.38	0.39
HCT	38.56	34.98	40.66	39.28	40.09	39.06	39.86
%	±2.04	6.97	1.70	2.27	2.33	1.09	0.89
MCV	62.4	56.4	54.1	57.2	55.3	57.8	54.3
fl	±1.0	2.6	1.1	1.6	1.0	1.6	1.2
MCH	22.63	21.86	20.46	21.76	20.76	21.60	20.65
pg	±0.31	0.83	0.40	0.88	0.47	0.55	0.52
MCHC	36.18	38.70	37.87	37.94	37.36	37.12	37.76
g/dl	±0.57	1.54	0.52	0.92	0.63	0.55	0.34
RET	2.28	0.36	0.16	0.44	0.29	0.52	0.13
%	±2.83	0.09	0.21	0.22	0.44	0.11	0.18
PLT	559.3	932.8	739.3	873.6	731.6	881.6	707.0
$x10^3/\mu l$	±152.2	111.8	96.8	67.1	117.4	129.1	114.7
WBC	4.47	4.22	4.17	4.90	5.78	5.52	4.50
$x10^3/\mu l$	±1.25	1.22	1.69	2.02	1.68	1.40	1.61
SEG	12.9	12.2	12.3	11.2	10.1	10.4	8.4
%	±4.8	4.9	4.8	7.9	3.2	3.2	3.9
BAN	0.0	0.0	0.0	0.0	0.1	0.0	0.0
%	±0.0	0.0	0.0	0.0	0.3	0.0	0.0
EOS	0.8	0.0	0.4	1.0	0.3	1.0	0.5
%	±0.9	0.0	0.5	1.4	0.7	1.0	0.8
LYM	86.3	87.8	87.1	87.8	89.3	88.4	91.1
%	±5.0	4.9	4.9	7.2	3.1	2.5	3.6
MON	0.0	0.0	0.2	0.0	0.1	0.0	0.0
%	±0.0	0.0	0.4	0.0	0.3	0.0	0.0

* Data are presented as the mean ± the standard deviation.

TABLE 7 (cont.): Hematology Summary*

	Females					
Group	30.0 mg/kg/day		60.0 mg/kg/day		90.0 mg/kg/day	
Day	28	90	28	90	28	90
n	5	8	5	10	5	9
RBC	7.102	7.303	6.870	7.026	6.878	7.253
$x10^6/\mu l$	±0.351	0.389	0.475	0.559	0.453	0.662
HGB	15.16	15.34	14.84	15.17	15.00	15.37
g/dl	±0.78	0.73	0.77	0.77	1.04	0.97
HCT	39.78	39.48	40.28	39.16	40.86	40.47
%	±3.06	2.07	3.06	2.10	3.17	2.45
MCV	56.0	53.9	58.4	54.1	59.2	55.1
fl	±3.0	1.6	1.8	1.2	1.6	0.9
MCH	21.28	20.91	21.56	20.90	21.64	20.83
pg	±0.68	0.36	0.81	0.34	0.56	0.33
MCHC	37.98	38.61@	36.72@	38.46	36.48@	37.83
g/dl	±0.86	0.55	1.27	0.45	0.72	0.70
RET	0.60	0.18	0.56	0.26	0.64	0.16
%	±0.45	0.23	0.22	0.31	0.38	0.22
PLT	952.4	719.6	927.2	700.3	878.4	743.6
$x10^3/\mu l$	±94.6	124.2	72.9	249.4	74.4	121.3
WBC	7.06	5.69	6.60	5.25	9.68@	4.32
$x10^3/\mu l$	±2.80	1.38	1.33	1.55	2.63	1.87
SEG	11.4	9.4	8.2	13.6	14.0	10.8
%	±3.9	5.1	3.8	7.8	3.4	3.3
BAN	0.0	0.0	0.0	0.0	0.0	0.0
%	±0.0	0.0	0.0	0.0	0.0	0.0
EOS	0.8	0.3	0.4	1.0	0.6	0.6
%	±1.1	0.5	0.5	0.9	1.3	0.7
LYM	87.8	90.3	91.4	85.3	85.4	88.7
%	±4.1	5.3	4.2	7.3	4.6	3.2
MON	0.0	0.1	0.0	0.1	0.2	0.0
%	±0.0	0.4	0.0	0.3	0.4	0.0

* Data are presented as the mean ± the standard deviation.
@ Significant difference from controls at $p \leq 0.05$.

TABLE 8: Percent Cholinesterase Inhibition*

Group (mg/kg/day)	Control	1.0	10.0	30.0	60.0	90.0
			Males Day 28			
ACHE	0.0	25.9	30.8	34.0	66.7	28.9
CHE	0.0	-3.8@	46.5	67.9	67.9	71.9
			Males Day 90			
ACHE	0.0	30.3	41.3	66.9	82.5	88.7
CHE	0.0	14.8	50.0	61.0	67.3	76.3
			Females Day 28			
ACHE	0.0	-7.9	18.5	38.3	49.3	60.6
CHE	0.0	-80.8	-16.5	4.9	34.5	36.9
			Females Day 90			
ACHE	0.0	73.6	78.3	82.7	85.4	95.4
CHE	0.0	12.7	27.0	51.0	57.1	64.8

* Percent inhibition calculated as [(mean baseline activity - normalized mean treated activity) ÷ mean baseline activity] x 100%.
Normalized mean treated activity calculated as (mean baseline activity ÷ mean control group activity) x mean treatment group activity.

@ Negative percent inhibition indicates treatment group activity level exceeded the baseline activity.

AChE were statistically significant for all male and female treatment groups at Day 90. At Day 28, the decreases in AChE were statistically significant only for female Groups 4, 5, and 6. The decreases in ChE were statistically significant for male Groups 3, 4, 5, and 6 at Days 28 and 90. For the females, statistically significant decreases in ChE were observed for Groups 4, 5, and 6 at Day 90. Percent inhibition ranged from ~5% to 76% (ChE) and ~18% to 95% (AChE).

Necropsy Findings

All gross and microscopic lesions were considered to be incidental findings commonly observed in Sprague-Dawley rats. No compound-related gross or microscopic lesions were observed. There were no microscopic lesions that were significantly different in severity from the control using the Kolmogorov-Smirnov two-tailed test. The pathology report is presented in Appendix O.

DISCUSSION

Doses of pyridostigmine that produced up to 76% cholinesterase inhibition in plasma and 95% acetylcholinesterase inhibition in erythrocytes did not have toxic effects other than those attributable to cholinergic stimulation. No consistent treatment-related changes attributable to pyridostigmine administration were observed in serum chemistry or hematology values during the 90-day study period. In addition, there were no mortalities or lesions noted at necropsy or on microscopic examination of tissues that could be attributed to pyridostigmine administration.

The clinical signs of toxicity observed were consistent with cholinergic stimulation following cholinesterase inhibition (14,15). Toxic signs attributable to excessive muscarinic stimulation included stains or material on various parts of the body (perianal, perioral, or periocular), diarrhea, and increased salivation. The nicotinic effects observed included hypertonia and tremors. The other behavioral signs and increased startle reflex may have been due to stimulation of the central nervous system as has been observed with other anti-ChE agents. Such signs are consistent with CNS signs such as confusion, ataxia, slurred speech, and loss of reflexes, which have been observed in humans exposed to anti-ChE agents (14).

The initial transient decrease in food consumption exhibited by Group 5 and 6 males, and Group 6 females may be attributed either to decreased acceptance of the pyridostigmine-treated diets or a toxic manifestation of the test compound. Reduced food consumption upon initial exposure to a test compound in the feed is often observed in toxicity studies, and is generally associated with the reduced palatability at the higher concentration of test compound. However, the possibility that decreased food consumption may have been induced by the pharmacologic activity of the test compound cannot be ruled out. Among the muscarinic effects associated with the therapeutic administration of pyridostigmine in humans are anorexia, nausea, vomiting, and abdominal cramps (14,16). Most patients eventually develop resistance to these muscarinic effects (14). Similar effects induced in animals of the high-dose groups in this study with the subsequent development of tolerance, could easily have contributed to transiently decreased food and water consumption, and correspondingly reduced weight gains. Increased food consumption, water consumption, and body weights observed among the remaining female treatment groups relative to the controls were already apparent at the end of quarantine, and may be attributed to differences in acclimation unrelated to administration of the test compound.

Pyridostigmine reduced plasma cholinesterase and erythrocyte acetylcholinesterase significantly ($p \leq 0.05$). Variations from the expected dose-response relationship could be attributed to several factors, the most important being that the large sample volume required for the cholinesterase determination precluded each animal from serving as its own baseline. Consequently, the percent cholinesterase inhibition for a particular treatment required normalizing the mean cholinesterase activity for baseline control animals obtained on Day 0 and the mean activity for the Day 28 or Day 90 concurrent control group. Other factors contributing to this variation may have been the small number of animals (n=5/group) for the Day 28 determinations, differences in age of the animals when activity was determined (7-8 weeks at Day 0, 11-12 weeks at Day 28, and 20-21 weeks at Day 90), and variations in the time interval from the last feeding episode to blood sample collection at necropsy. Pyridostigmine must be administered every 3 to 6 hours to achieve reasonably constant levels of pharmacologic activity in man; the elimination half-life of pyridostigmine in man has been reported to be 1.9 ±0.2 hours (17), as compared to 24.8 minutes in the rat (18). Therefore, in order to achieve constant levels of cholinesterase inhibition in the rat, the required frequency of oral dosing would be expected to be considerably greater than that in man. Consequently, in this

study, levels of cholinesterase inhibition would naturally fluctuate as a result of the feeding frequency. These fluctuations in cholinesterase inhibition would also increase variability in the measured dose-response.

CONCLUSION

Administration of pyridostigmine at doses of 1 to 90 mg/kg/day did not cause any appreciable toxicologic effects. Transient reductions in food consumption and rate of growth observed at the high-dose levels, and clinical signs of cholinergic stimulation due to subchronic inhibition of plasma ChE and erythrocyte AChE were present but were considered to be mild and nondebilitating.

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Appendix A: CHEMICAL DATA

Chemical Name: Pyridostigmine bromide

Other Names: 3-[[(Dimethylamino)carbamyl]oxy]-1-methylpyridinium bromide, 3-hydroxy-1-methylpyridinium bromide dimethylcarbamate, 1-methyl-3-hydroxypyridinium bromide dimethylcarbamate, 3-(dimethylcarbamyloxy)-1-methylpyridinium bromide

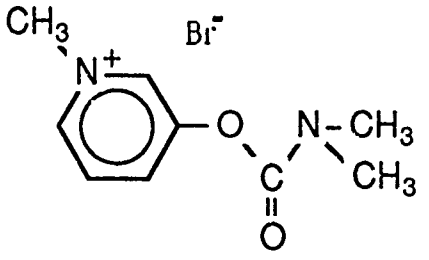
Chemical Abstracts Registry Number: 101-26-8

Lot Number: 590034

LAIR Code Number: TW71A

WRAIR Code Number: WR-250710AF

Chemical Structure:



Molecular Formula: $C_9H_{13}BrN_2O_2$

Molecular Weight: 261.13

Analytical Data:

The test compound was analyzed by the sponsors using HPLC, elemental analysis, and UV spectroscopy.[1] This data verified the identity of the compound and provided the following estimates of purity: 99.6% (by HPLC), 98% (by elemental bromide), and 100% (by UV spectroscopy).

Pyridostigmine bromide was analyzed in this lab by NMR[2] and HPLC[3].

Appendix A (cont.): CHEMICAL DATA

NMR (300 MHz, D_2O): d 3.02, 3.16 (singlets, $(CH_3)_2$-N-, 6 H); 4.43 (singlet, CH_3-N(pyr), 3H); 8.09 (quartet, J = 8.6, 6.3 Hz, O-C=CH-C*H*=CH-N, 1 H); 8.39 (doublet, J = 9.0 Hz, O-C=C*H*-CH-, 1 H); 8.71 (doublet, J = 6.0 Hz, CH=C*H*-N, 1 H); 8.86 (singlet, O-C=C*H*-N, 1 H). No other signals were observed in the spectrum.

HPLC analysis of the compound was performed using a Hewlett-Packard 1090 HPLC equipped with a diode array detector. The compound was chromatographed under the following conditions: column, silica (Brownlee Labs, Inc., 4.6 x 100 mm); mobile phase, 80% buffer (0.01 M heptane sulfonic acid, 0.01 M sodium dihydrogen phosphate, 0.0025 M tetramethylammonium chloride, pH adjusted to 3 with sulfuric acid)/20% acetonitrile; flow, 1.5 ml/min; wavelength monitored, 269 nm. Under these conditions, pyridostigmine bromide eluted as one peak at 2.4 min. No other peaks were present in the chromatogram.

The data obtained in our lab confirm the identity and high purity of the test compound.

Source: Mr. William Ellis
Division of Experimental Therapeutics
Walter Reed Army Institute of Research
Washington, DC
Requested by LTC William Ritter, WRAIR

---

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[2] Wheeler CR. Toxicity testing of antidotes of chemical warfare agents. Laboratory notebook #85-12-024.1, p. 70-71. Letterman Army Institute of Research, Presidio of San Francisco, CA.

[3] *Ibid.* p. 72-74.

Appendix B: ANIMAL DATA

Species: *Rattus norvegicus*

Strain: Sprague-Dawley

Source: Charles River Laboratories, Inc.
Charles River Portage
Shaver Road
Portage, Michigan 49081

Sex: Male and female

Date of birth: Males - 15 September 1986
Females - 17 October 1986

Method of randomization: Males - Random number generating program (LAIR SOP OP-ISG-21)
Females - Weight bias, stratified animal allocation (TOXSYS Animal Allocation Program, LAIR SOP OP-ISG-24).

Animals in each group: 15 male and 15 female animals

Condition of animals at start of study: Normal

Body weight range at start of dosing: 151 - 287 g

Identification procedures: Tail tattoo (SOP OP-ARG-1)

Pretest conditioning: Quarantine/acclimation; males from 21 October - 3 November 1986, females from 25 November - 9 December 1986

Justification: The laboratory rat has proven to be a sensitive and reliable system for sub-chronic oral toxicity determination.

Appendix C: SUBCHRONIC TOXICITY TESTING IN RODENTS

TITLE: Subchronic Toxicity Testing in Rodents

SCOPE: This subchronic toxicity study is designed to assess the toxic potential of a test substance when administered to a rodent for between 28 and 180 consecutive days. It is conducted in compliance with the Toxic Substance Control Act as administered by the EPA. This study will also be conducted in compliance with the Good Laboratory Practices regulation promulgated by the FDA.

REFERENCES:

1. EPA, Toxic Substances Control, GLP Standards; Final Rule, (40 CFR 792) 29 Nov 83, (48 FR 53922-53944).

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PROCEDURE:

A. Study Design

1. Species: A recognized strain of the laboratory rodent (e.g., rat; Sprague-Dawley, Fisher-344) will be purchased from a licensed dealer by the Division of Animal Care and Service, LAIR. Generally the strain selected should be one which will be utilized in chronic studies.

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

2. Age and Sex: Equal number of males and females will be tested. Animals should receive the initial dose before attaining eight weeks of age.

3. Number of Animals: Each group, treatment and concurrent control, must contain a minimum of 10 animals/sex/group. If interim sacrifices are required the number of animals will be increased by the number scheduled for sacrifice.

4. Quarantine: Animals will be quarantined for two weeks in the GLP Suite for environmental acclimatization and detection of disease/parasites/poor health. Randomly selected animals (2% of total) will be sacrificed by the pathologists for quality control.

5. Animal Identification and Randomization: Animals will be identified by tail tattoo and randomly assigned to control and treatment groups. Randomization will be by a weight stratification procedure.

6. Husbandry: Animals will be housed individually in shoe-box cages in the GLP Suite. Temperature in the GLP Suite will be maintained in the range of 72 - 76' F with relative humidity of 40-60%. A 12 hour light/dark cycle will be utilized. Temperature and relative humidity will be recorded. Animals will be fed batch certified rodent chow ad libitum and provided deionized reverse osmosis treated water ad libitum. The deionized reverse osmosis water is periodically analyzed on a retrospective basis. None of the contaminants in food and water are reasonably expected to be of sufficient titre as to interfere with conduct of the proposed studies.

7. Control Group(s): A vehicle control group will be used, and in cases where the effects of the vehicle are unknown, an untreated control group will also be tested.

8. Treatment Groups: At least three dose levels will be tested. The highest dose level should produce toxicological or pharmacological effect but produce no more than 10 percent lethality. This dose should be higher than that expected for human exposure. The low dose should not produce evidence of toxicity. The intermediate dose should be a multiple of the low dose and provide an estimate of the dose-response relationship. Generally, a limit dose of 1000 mg/kg will be the maximum dose level used, unless higher dose levels are justified.

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

9. Duration: The test substance will be administered for between 28 and 180 consecutive days.

10. Administration of Test Substance: The test substance will be administered in the diet at a constant concentration (ppm) unless oral gavage or diet administration (constant dose, mg/kg) is required by the Sponsor. The constant dose procedures requires weekly adjustment of dose because of changing body weights. Other routes, such as subcutaneous,dermal patch, I.V., etc., may be used if they are more representative of the potential route of exposure or administration.

11. Test Substance Analysis and Stability: Physio-chemical data on the batch or lot of the test substance used in the study will be provided by the sponsor as well as an analytical profile of major constituents and/or contaminants/impurities. Safety precautions will also be provided by the sponsor. Stability of the test substance in the diet (vehicle) and homogeneity for the range of concentrations used will be determined at the initiation of the study. Additionally, assays for homogenicity will be run at selected intervals during conduct of the study. Assays for concentration will be conducted on each dosing mixture prepared.

12. Quality Assurance: The LAIR Quality Assurance Unit will audit the protocol, in-life phase, and final report for compliance with GLP procedures.

B. Study Conduct

1. Observations: All toxicological and pharmacological signs will be recorded daily, including time of onset, intensity and duration. Food and water consumption will be measured and animals will be weighed weekly.

2. Clinical Laboratory Testing: At least 5 animals/sex/group will be bled at selected intervals during the study and at termination of the study. The same animals should be bled on each occasion if possible. At the discretion of the sponsor and/or study director, clinical laboratory testing may be done by serial sacrifice.

a. Hematologic evaluation - The PCV, Hgb, RBC, WBC, differential, MCV, MCHC, and platelets determinations are required. If signs of anemia are present, reticulocyte counts will be performed on whole anticoagulated blood.

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

b. Blood Chemistry - Ca, Na, K, Mg, Cu, total Fe, LDH, serum ALT, serum AST, glucose, BUN, direct/total bilirubin, A/G ratio, cholesterol, albumin, globulin, total protein, Cl, uric acid, creatinine, CPK, methemoglobin, P, and triglycerides will be measured.

c. Cholinesterase inhibition - If the sponsor indicates that the test substance may inhibit acetylcholinesterase activity, plasma and erythrocyte acetylcholinesterase activity will be monitored at selected intervals during the study.

d. Urinalysis - If applicable the following will be measured before the initiation of dosing, during the seventh week, and near the termination of the study:

1. specific gravity (osmolarity)
2. pH
3. protein
4. ketones
5. glucose
6. bilirubin
7. urobilinogen
8. occult blood
9. microscopic observation of casts, etc.

3. Moribund animals should be sacrificed and a complete necropsy and tissue/blood collection performed, to lessen the likelihood of unobserved death and post mortem autolysis. Animals found dead will be subjected to a gross necropsy. Histopathology on these animals will be at the discretion of the Pathologist.

4. Gross Necropsy

a. All animals are subjected to gross necropsy and examination of external surface, all orifices, cranial cavity, external and cut surfaces of the brain and spinal cord, the thoracic, abdominal and pelvic cavities and their viscera; the cervical tissues and organs, and carcass.

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

b. The following tissues are weighed:

liver

kidneys

inrenals

heart

gonads

brain

5. Histopathology

a. Animals in vehicle and cage control and high dose groups will have histopathology performed on:

brain (3 levels)

eye

pituitary

salivary gland

heart

thymus

thyroid/parathyroid

lung w/mainstem bronchi

trachea

esophagus

stomach

small and large intestine

adrenals

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

pancreas

liver

kidneys

urinary bladder

testes

prostate

ovaries

uterine horn and corpus

spleen

bone (with marrow) from sternebrae, vertebrae, tibio-femoral joint

skeletal muscle

all gross lesions

b. Low and intermediate dose groups will have histopathology performed on liver, lung, kidney, heart, any gross lesion and any target organ (determined from either the high dose or from laboratory tests).

6. Data Reporting and Evaluation

a. Animal records will be arranged by dose level and sex. All means accompanied by standard deviation and/or standard error of the mean will be reported.

b. In tabular form data must be provided, as follows, for each animal.

1. Identification number

2. Status at and date of death

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

3. Age at beginning of study

c. Toxic, pharmacologic and behavioral effects for each animal and each group.

1. A list of each sign of toxicity affecting any animal

2. Number of animals affected

3. The median time for development of such responses

4. Weekly survival and sacrifice data

d. Food consumption and body weight data:' for each animal, the following should be tabulated:

1. Identification number

2. Weekly measured food consumption

3. Weekly body weight

4. Food and body weight means for each group

5. If compound mixed with diet, weekly compound consumption per group.

e. Clinical laboratory tests results:

1. Rationale for timing if different from this SOP.

2. Rationale and method for selection of animals for clinical laboratory tests.

3. Results by animal and by group.

f. Gross anatomy results by test group in tabular form

1. Data on gross abnormalities, description by animal and group.

2. For each individual, body weight, organ weight, and organ to body weight ratio, mean weights of each type of organ, mean organ to body weight ratio.

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

g. Histopathology data arranged by test group:

1. For each animal, its identification number and complete description and diagnosis of every lesion in the animal. Abnormalities observed repeatedly need to be described only once and may subsequently be supplied by reference, with any individual variation noted as necessary.

2. For each animal a table or paragraph listing tissues found to be normal.

3. If a grading system is used, a description of the system.

4. Counts and incidence of lesions by test groups. In tabular form for each test group:

a. The number of animals at the start, and number of animals in which any lesion was found.

b. The number affected by each different type of lesion, the number examined for each type, the percentage of animals examined that were affected.

c. The number of different types of lesions.

5. Observance of tumors will necessitate the inclusion of a complete description and diagnosis of each tumor.

h. Data Evaluation: An evaluation of the test results, including the statistical analyses, based on clinical findings, gross necropsy findings and histopathology results will be made. It will include the evaluation of the relationship of the animal's exposure to the test substance and the incidence and severity of all abnormalities, gross and histological changes, organ weight changes, effects on mortality and other toxic effects. It should include dose response curves for effects that appear compound related and description of statistical methods.

Appendix C (cont.): SUBCHRONIC TOXICITY TESTING IN RODENTS

Approved: 7 APR 87 (Date)

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Appendix D: HISTORICAL LISTING OF STUDY EVENTS

Date	Event
21 Oct 86	Male animals arrived at LAIR. They were sexed, observed for illness, weighed, and caged in the GLP Suite.
22 Oct 86	Four male animals were submitted for quality control necropsy.
22,24, 29 Oct 86	Male animals were tattooed.
22 Oct - 3 Nov 86	Male animals were checked daily.
28 Oct 86	Male animals were weighed and food and water consumption monitored (feeders and water bottles weighed).
29 Oct,1 Dec 86,5 Jan,2,3 Feb,10 Mar 87	Ophthalmic examinations were performed at baseline and within 1 week prior to sacrifice for males and females.
4 Nov 86	Male animals were removed from quarantine and weighed, dietary concentrations were calculated, and diet containing test compound was started. Ten baseline control males were submitted for necropsy, hematology, serology, and cholinesterase determinations.
4 Nov 86 - 11 Mar 87	Observations were conducted twice daily.
11,18,25 Nov, 2,9,16,23,30 Dec 86,6,13, 20,27 Jan,3 Feb 87	Males were observed and weighed, and water bottles and feeders were weighed. Diet requirements were recalculated and new feed mixes prepared. Feeders were changed to new mix.
25 Nov 86	Female animals arrived at LAIR. They were sexed, observed for illness, weighed, and caged in the GLP Suite.
26 Nov 86	Female animals were tattooed. Four animals were submitted for quality control necropsy.
26 Nov - 9 Dec 86	Female animals were checked daily.

Appendix D (cont.): HISTORICAL LISTING OF STUDY EVENTS

Date	Event
1 Dec 86	Female animals were weighed.
2,3 Dec 86	Five males per group were submitted for necropsy, hematology, serology, and cholinesterase determinations.
3 Dec 86	Food and water consumption monitored for females (feeders and water bottles weighed).
10 Dec 86	Female animals were removed from quarantine and weighed, dietary concentrations were calculated, and diet containing test compound was started. Ten baseline control females were submitted for necropsy, hematology, serology, and cholinesterase determinations.
17,24,31 Dec 86,7,14,21,28 Jan,4,11,18,25 Feb,4,11 Mar 87	Females were observed and weighed, and water bottles and feeders were weighed. Diet requirements were recalculated and new feed mixes prepared. Feeders were changed to new mix.
7 Jan 87	Five females per group were submitted for necropsy, hematology, serology, and cholinesterase determinations.
3,4,5 Feb 87	Ten males per group were submitted for necropsy, hematology, serology, and cholinesterase determinations.
11,12 Mar 87	Ten females per group were submitted for necropsy, hematology, serology, and cholinesterase determinations.

Appendix E: PROCEDURES FOR DIET PREPARATION

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20 May 1988
REPLACES: 1 November 1986

TITLE: Diet Preparation for Feeding Studies

SCOPE: These procedures comply with the FDA and EPA GLP Regulations and are applicable to preparation of diets for studies in which the test chemical is administered in the food.

REFERENCES:

1. EPA, Toxic Substances Control, GLP Standards (40 CFR 792) Final Rule, 29 Nov 83, (48 FR 53922-53944).

2. EPA, Pesticide Programs, GLP Standards (40 CFR 160) Final Rule, 29 Nov 83 (48 FR 53946-53969).

3. FDA, Nonclinical Laboratory Studies (21 CFR 58) Final Rule, 22 Dec 78 (43 FR 59986-60025).

4. EPA, Health effects test guidelines. Office of Pesticides and Toxic Substances. EPA 560/6-82-001.

5. Chan PK, O`Hara GP, Hayes AW. Principles and methods for acute and subchronic toxicity. In: Hayes AW ed. Principles and methods of toxicology. New York: Raven Press, 1982: 1-52.

6. Kuhn GO, Rollheiser JJ, Schworer BA, Jameson CW. Methods Development for Mixing Chemicals in Rodent Feed. In: Jameson CW, Waters DB, eds. Chemistry for Toxicity Testing. Boston: Butterworth Publishers, 1984: 59-81.

7. Paget GE, Thomson R. Standard operating procedures in toxicology. Baltimore: University Park Press, 1979: 123-158.

8. Stevens KR, Gallo MA. Practical considerations in the conduct of chronic toxicity studies. In: Hayes AW ed. Principles and methods of toxicology. New York: Raven Press, 1982: 53-77.

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

INTRODUCTION:

Overview

Diet preparation consists of four stages: inital testing, target concentration calculations, premix preparation and diet preparation. The time required for each of these stages depends in part on the methods used and on the number of diets prepared. From start to finish, diet preparation for one feeding period can take from one to four days.

Safety Precautions

Certain precautions should be taken to prevent worker exposure and contamination of other areas outside the diet mixing room when preparing the premix and the diet. People preparing diet should be familiar with LAIR SOP OP-STX-69, "Safety Procedures for Handling of Test Compound and Positive Control Carcinogens". The risk of exposure when making premix in the jar mill may not be as great as when making diet in the open mixers since it is not as likely to become airborne, but one should still be cautious when handling the premix since the concentration of the test chemical is much greater. With highly toxic chemicals or suspect carcinogens, individuals preparing the premix should at least wear gloves, disposable gown, and shoe coverings. Individuals preparing the diet should also wear a mask and head covering. The type of gloves, gown, and mask worn will depend on the physical nature of the chemical and the degree of toxicity or carcinogenicity of the chemical. With chemicals of low toxicity these measures are optional. The safety officer for the group should be consulted if there are any questions regarding the appropriate clothing to wear. The protective clothing should not be worn outside the diet mixing area to prevent contamination of other areas. To minimize contamination, it is recommended that the door to the diet mixing room be closed and locked during diet preparation. The jar mill and open mixers should be used in the hood with the blower on.

Cleaning up is also critical for keeping contamination to a minimum. After completing the diet preparation, the equipment should be cleaned including the jar mills, grinding pellets, mixing bowls, beaters, V-type blender, weighing containers, scoops and spatulas. In addition, the counter tops should be cleaned and the floor swept or vacuumed. If a vacuum cleaner is used it should have a HEPA filter on the exhaust. The floor should be cleaned with a wet mop as needed.

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

PROCEDURES:

I. Initial Testing

Before a feeding study starts the following needs to be done: validate the adequacy of the cleaning procedures, determine the stability of the test compound in the feed, and verify the homogeneity of the test compound/feed mixtures.

A. Validating the Cleaning Procedures

1. After mixing the test compound with the feed at the highest concentration to be used during a study, wash the blender or mixer. The recommended procedure for washing the blenders/mixers is to fill them about a third full with water and add approximately 10-30 mls of laboratory glassware detergent. Blenders, like the Patterson-Kelley blenders, which have mixing containers that cannot be easily removed for cleaning should be turned on for no more than 1 minute after adding the soapy water. Be sure the blender is sealed tightly so that the water does not leak out. The mixers or blenders should then be rinsed at least twice with water (the volume equal to the wash volume). The blenders will be turned on for approximately 1 minute per rinse.

2. These procedures can be modified. The procedures used to clean the mixers and blenders should be documented in the cleaning log book each time they are cleaned, regardless of the method used. The type of detergent, solvent, and number of rinses should be recorded.

3. After cleaning the mixer or blender, it will be checked for residual test compound. A small amount (10-50 mls) of an appropriate solvent (water, methanol, ethanol, isopropanpol, etc.) will be added. The blender or mixer will be turned on for no more than 1 minute. The solvent wash will be analyzed by appropriate method (HPLC, GC, etc.). The solvent and method of analysis used will be documented.

B. Stability Determination

The stability of the test compound in the feed should be determined for a period of time no less than the time from which the diet is prepared to the time it is removed from the feeders. The stability should be tested at concentrations which bracket the range of concentrations

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

that will be used in the study. For additional information refer to OP-STX-95, "Analytical Chemistry Requirements for Toxicity Testing of Chemicals."

C. Homogeneity Verification

The adequacy of the mixing procedures is verified by preparing the test compound/feed mixtures at concentrations which bracket the concentrations to be used in the study. The volume of the mixtures prepared should also bracket the volumes to be used in the study. Homogeneity is tested by removing samples from the top, middle, and bottom of the mixing bowl or from each of the three ports of the Patterson-Kelly blenders. Samples will be analyzed by the appropriate method for the test compound (HPLC, GC, etc.). The concentrations of each sample should deviate no more than 10% from the mean of the three samples. For additional information refer to OP-STX-95, "Analytical Chemistry Requirements for Toxicity Testing of Chemicals." Homogeneity should be re-checked periodically during the course of the study.

II. Calculation of Target Concentration for Diets

The time required for calculating the target concentration for each dose group can vary depending on whether they are done automatically by the TOXSYS programs or manually. If the TOXSYS programs are used, the calculations can be done on the same day the diets are blended. If the calculations are performed manually, they should to be done at least one day before the diets are blended.

A. Place the animals on the powdered feed (control diet) during quarantine. Record feeder weights on TOXSYS IAW SOP OP-ISG-17, "Standard Procedures for Acquiring Toxicology Experiment Data Using a TOXSYS Data Collection Terminal" or manually (Figure 1). If recorded manually, calculate the net food consumed for each animal by subtracting the old feeder weight from the previous new feeder weight. Record the net food consumed on the form in Figure 1.

B. Determine the mean daily food consumption for each group during the baseline period. If TOXSYS is used, the calculations described in steps B - F are done automatically with the DIET Program (SOP OP-ISG-36, Standard Procedures for Computing Diet Mix Concentration on a TOXSYS Data Collection Terminal) on the TOXCART or with the DIETPREP program (SOP OP-ISG-33, Standard Procedures for Reporting Animal Data Base Records on the LAIR Central Computer) on the mainframe computer. If the calculations are done manually,

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

record your results from steps B - F on the form in Figure 2. To calculate the mean daily food consumption manually, average the net food consumed by all the animals in a group and divide that by the number of days in the dose period.

C. Weigh the animals at the end of the same week that baseline food consumption data are collected during quarantine. Use the data to calculate the mean body weights for each group.

D. Multiply the dose level (mg/kg/day) for each group by the mean body weight (kg) and divide by the corresponding mean daily food consumption (g/day) to obtain the target concentration (mg/g) of the diet for that group.

E. Multiply the target concentration by the correction factor to allow for changes in the ratio of the mean body weight and the mean food consumption that occur as a result of growth. The correction factor is based on historical data from animals of the same species and strain which are of similar age and have been fed a similar diet. If no data is available set the correction factor equal to 1 which will not affect the target concentration.

F. At the end of each week or feeding period recalculate the mean daily food consumption and the mean body weight for each group based on the feeder weights and body weights recorded during that period.

G. Recalculate the target concentration for each group using the new mean daily food consumption and new mean body weight.

H. If an animal dies during a feeding period, do not use it in the calculations. In addition, do not include animals whose food consumption is questionable due to some unusual circumstance, such as significant spillage of food or wet food.

III. Premix Preparation

The premix may be made several ways. If the test chemical is a solid that is stable in the feed, then a premix can be made up several days in advance and can be used with all the diets. If the dosing range is too large (greater than a 100 fold difference between low and high dose levels), then 2 or more premixes may be needed. In this situation, making separate premixes for each diet may be easier. Procedures for both methods are given below.

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

A. Preparation of a Single Premix for All Diets

If a single premix is prepared for all diets, then the premix should be prepared at least one day prior to diet preparation. The time required for premix preparation will depend on whether the chemical needs to be ground in the jar mill. If the jar mill is used, premix preparation may require 4 - 8 hours.

1. Calculation of Premix Concentration

   a. For the first dose period approximate the diet concentration for the each dose group by using estimates of the mean daily food consumption and the mean body weight. For subsequent dose periods use the diet concentrations from the previous period. Select a concentration for the premix that is at least 2 - 3 times greater than the diet concentration of the high dose group.

   b. Calculate the amount of diet needed for each group by multiplying the number of animals per group times the mean daily food consumption times the number of days per period times 1.5 to allow for wastage.

   c. Approximate the amount of test chemical needed by multiplying the amount of diet needed for each group (g) by its concentration.

   d. To determine the amount of premix needed, divide the amount of test chemical needed (g) by the concentration of the premix (mg/g). Add at least another one third more to this amount to allow for increases in the diet concentrations due to animal growth.

2. Blending of Premix

   a. Calibrate the balances(s) to be used for preparing the premix and record the weights in the appropriate log book(s). Record the LAIR ID number (4-digit number) of the balance on the form in Figure 3.

   b. Weigh out the desired amount of test chemical on the balance. Record the weight and lot number of the test chemical on the form in Figure 3.

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

c. Transfer the test chemical to the bowl of a mixer. NOTE: If the test chemical is coarsely ground or in clumps, transfer it to the porcelain jar of the jar mill. Add the porcelain grinding pellets. Grind the test chemical alone for at least 15 minutes.

d. Weigh out the amount of feed needed to achieve the desired concentration. Record the weight and the lot number of the feed. Record the LAIR ID number for the balance, if different from the one above.

e. Add a portion of the feed roughly equal to the weight of the test chemical to the mixer or jar mill. Stir with a spatula. If the premix is prepared in the jar mill, grind at least 15 minutes. Repeat this step, doubling the amount of feed added, until all the feed has been added.

f. Mix the premix with the mixer for 15 minutes in the hood. If the jar mill is used, grind another 15 minutes after the last addition of feed.

g. Remove at least a 10 g sample from the premix. Part of the sample is for analysis and the remainder is for archival.

h. Transfer the rest of the premix to a plastic bag and label it clearly with the study number, date, chemical, concentration and your initials. If the premix was prepared in the jar mill, be sure to remove all of the grinding pellets from the premix since they can be harmful to the blender if not detected before adding the premix to the feed (not to mention its effect on the concentration). The easiest way to remove them is to sift the premix through a large mesh sieve when transfering it to the bag.

B. Preparation of Separate Premixes for Each Diet

This method is recommended when using a liquid, hygroscopic, or unstable test chemical or when the range of dose levels is large.

1. Blending of Premixes with Solid Chemicals

a. Calibrate balance(s) to be used in premix

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

preparation and record weights in log book(s). Record the LAIR ID number(s) (4-digit number) of the balance(s) on the form in Figure 4.

b. Record lot numbers of the test chemical and feed on the form in Figure 4.

c. Accurately weigh out the test chemical and transfer it to a large beaker (600-2000 ml) or a large mortar if the chemical is coarsely ground or in clumps. Record the weight on the form.

d. Weight out the total amount of feed to be added to the premix and record the weight on the form. The total weight of the premix should be at least 10% of the total weight of the diet.

e. From the feed that has been weighed out, take an amount that is roughly equal to the weight of the chemical and add it to the chemical, mixing or grinding afterwards.

f. Add more feed and mix or grind in, doubling the amount of feed added each time until all the feed has been added.

g. Transfer to the bowl for the small mixer and mix at low speed for at least 5 minutes in the hood.

2. Blending of Premixes with Liquid or Hygroscopic Chemicals

a. Calibrate balances(s) to be used in premix preparation and record weights in log book(s). Record the LAIR ID number(s) (4-digit number) of the balance(s) on the form in Figure 4.

b. Record lot numbers of the test chemical and feed on the form in Figure 4.

c. Accurately weight out test chemical into a small (50-200 ml) beaker. Record weight on the form. NOTE: If the chemical has large clumps or is coarsely ground, weight out the chemical on a weight boat and transfer to a mortar. Grind the chemical alone before adding any feed.

d. Weight out the total amount of feed to be

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

added to the premix and record the weight on the form. The total weight of the premix should be at least 10% of the total weight of the diet.

e. Transfer roughly 100 g of the feed that has been weighed to a USS No. 100 mesh sieve and shake until approximately 10g of feed flour have been collected.

f. Add approximately 1 g of feed flour to the beaker or mortar containing the test chemical and mix or grind. Continue to add 1-2 g increments of flour until all the feed flour has been added. If a weigh boat was used, add the increments of feed to the weigh boat first. Stir with spatula and transfer to the mortar.

g. Transfer the mixture to the bowl for the small mixer. Add the coarse feed left on the sieve in increments of 25-50 g, stirring the coarse feed in the beaker or mortar first before adding to the bowl. Stir with a spatula after each addition.

h. Add the remaining feed in increments of roughly 100 g, stirring with a spatula after each addition.

i. Mix for at least 5 minutes on low speed in the hood.

IV. Blending of Diets

The type of blender used will depend on the toxicity/carcinogenicity of the test chemical. If the chemical is highly toxic or suspected of being carcinogenic, the diet should be prepared in the Patterson-Kelley V-type blender which is closed. Should it be necessary to use an open blender like the Hobart with a highly toxic/carcinogenic test chemical, use the blendein the hood. If an open blender is used with a low or moderately toxic chemical, place a large (preferably clear) plastic garbage bag over the blender when mixing to minimize the amount of diet that becomes airborne during mixing.

Each diet requires at least 45 minutes to an hour to prepare, allowingfor set-up and clean-up time. Depending on how many diets there are to prepare, it may require more than one day to complete this stage.

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

A. Calibrate the balance(s) to be used for diet preparation and record weights in the appropriate log book.

B. Calculate the amount of feed that should be added to the premix to get the desired concentration and divide in half. Weigh out the feed into two separate containers (i.e., one half of total into each). Record the weights on the form in Figure 5. Record the lot number and the LAIR ID number(s) (4-digit number) for the balance(s) on the form, too.

C. If using a single premix prepared ahead of time, weigh out the desired amount of premix and record it on the form. Record the date of the premix and the balance used (if different from the one above).

D. The procedure for mixing the diet will depend on the blender selected.

1. Hobart or Open Type of Blenders

a. Transfer half of the feed to the mixing bowl. Add the premix on top of the feed in the mixing bowl, then add the other half of the feed on top of the premix.

b. Mix the diet in the mixer for at least 15 minutes.

2. Patterson-Kelley V-Type Blenders

a. Transfer half of the feed to the blender shell. Load the blender with the two ports pointing upwards. Make sure the bottom port is sealed tightly before loading. Spread the feed evenly in the bottom of the blender. Add the premix in roughly equal portions to each port and spread it evenly over the feed. Add the remaing feed in a even layer over the premix. Seal the lids tightly on the top ports.

b. Mix the diet in the blender for 15 minutes, using the intensifier bar only during the first 5 minutes.

E. Remove at least a 10 g sample from each diet. Part of the sample is for analysis and the remainder is for archival.

F. Transfer the rest of the diet to a plastic bag and

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

label it clearly with the study number, date, chemical, concentration and your initials. To aid in identification the bag may be color coded with tape for the group and sex.

Approved: 27 MAY88
(Date)

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Chief, Division of Toxicology

Certified: 27 May 88
(Date)

Carolyn M. Lewis
CAROLYN M. LEWIS, MS
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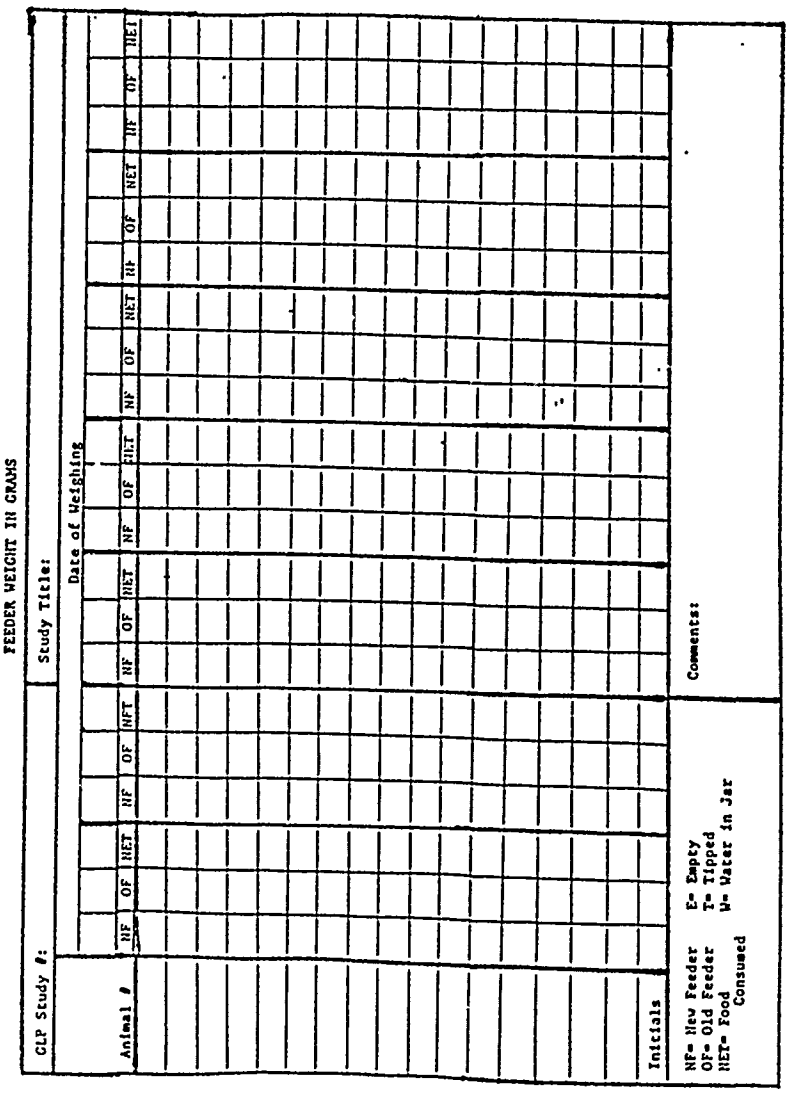
Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

Figure 1



Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

Figure 2

GLP Study #_____ Date_____

CALCULATIONS FOR TARGET CONCENTRATION OF DIET

Group #_____ Dose Level_____mg/kg/day

Sex_____ For Dates_____to_____

1. Mean Daily Food Consumption (MDFC)

   = _____ g/day

2. Mean Body Weight (MBW)

   = _____ kg

3. Target Concentration (TC)

   = Dose level X MBW ÷ MDFC = _____ mg/g

4. Correction Factor (CF) - Optional

   = _____

5. Target Concentration Adjusted for Growth - Optional

   = CF X TC = _____ mg/g

Comments:

Prepared by_____

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

Figure 3

GLP Study #_____ Date_____

BLENDING OF A SINGLE PREMIX FOR ALL DIETS

1. Test Compound

   Lot No(s). (if available) _____

   _____

   Weight _____ g

   LAIR ID # of Balance Used _____

2. Feed

   Lot No(s). _____

   _____

   Weight _____g

   LAIR ID # of Balance Used _____

Comments:

Prepared by _____

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

Figure 4

GLP Study #______________ Date________________

BLENDING OF SEPARATE PREMIXES FOR EACH DIET

Lot No(s) of Test Chemical________________________

____

Lot No(s). of Feed ________________________

____

LAIR ID No(s). of Balance(s) Used ________________

____

Group #______ Sex______	Group #______ Sex______
Conc.________mg/g Batch #____	Conc.________mg/g Batch #____
Wt. of Chemical________________g	Wt. of Chemical________________g
Wt. of Feed________________g	Wt. of Feed________________g
Group #______ Sex______	Group #______ Sex______
Conc.________mg/g Batch #____	Conc.________mg/g Batch #____
Wt. of Chemical________________g	Wt. of Chemical________________g
Wt. of Feed________________g	Wt. of Feed________________g
Group #______ Sex______	Group #______ Sex______
Conc.________mg/g Batch #____	Conc.________mg/g Batch #____
Wt. of Chemical________________g	Wt. of Chemical________________g
Wt. of Feed________________g	Wt. of Feed________________g

Prepared by ________________

Appendix E (cont.): PROCEDURES FOR DIET PREPARATION

Figure 5

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GLP Study #__________ Date__________

BLENDING OF DIETS

Lot No(s). of Feed ____________________

____

Date(s) Premix Prepared ____________________

____

LAIR ID No(s). of Balance(s) Used __________

____

Group #____ Sex____	Group #____ Sex____
Conc.____mg/g Batch #____	Conc.____mg/g Batch #____
Wt. of Premix________g	Wt. of Premix________g
Wt. of Feed________g	Wt. of Feed________g
________g	________g
Group #____ Sex____	Group #____ Sex____
Conc.____mg/g Batch #____	Conc.____mg/g Batch #____
Wt. of Premix________g	Wt. of Premix________g
Wt. of Feed________g	Wt. of Feed________g
________g	________g
Group #____ Sex____	Group #____ Sex____
Conc.____mg/g Batch #____	Conc.____mg/g Batch #____
Wt. of Premix________g	Wt. of Premix________g
Wt. of Feed________g	Wt. of Feed________g
________g	________g

Prepared by __________

Appendix F: ANALYSIS OF FEED MIXTURES

Feed mixtures containing pyridostigmine bromide (PYR) were prepared for GLP Study 86005 to provide dose levels of 1, 10, 30, 60, and 90 mg/kg body weight/day. PYR was determined to be stable in the diet for at least 8 days. New diets were prepared weekly to compensate for changes in food consumption and body weights due to growth. Male and female diets were prepared separately due to differences in body weight and food consumption. The target concentration of PYR in the feed mixtures ranged from 0.011 to 2.590 mg PYR/g feed.

Materials

Pyridostigmine bromide (Lot No. 590034) was supplied by Walter Reed Army Institute of Research (Washington, DC). Certified Rodent Chow #5002 (Lot Nos. JULY10861AMEAL, SEP03862AMEAL, SEP05862DMEAL, OCT03861EMEAL, JULY22861DMEAL, NOV13862CMEAL, NOV05861BMEAL, DEC04862EMEAL, JAN05871BMEAL, DEC16862DMEAL, FEB04872BMEAL, FEB26871DMEAL) was obtained from Ralston Purina (St. Louis, MO). All other chemicals were reagent grade. Tetramethylammonium chloride and 1-heptanesulfonic acid, sodium salt, were obtained from Aldrich Chemical Company (Milwaukee, WI); sodium phosphate monobasic was obtained from J.T. Baker Chemical Company (Phillipsburg, NJ). The water used in preparation of all HPLC solutions was deionized, distilled, and purified of organics using an Organicpure Water Purifier (Barnstead, Boston, MA).

The chromatographic system consisted of a Hewlett-Packard 1090 liquid chromatograph with diode array detector, an 85 B Personal Computer, a DPU Multichannel Integrator, and a ThinkJet Printer (Santa Clara, CA). Separations were obtained on a Brownlee silica column (4.6 x 100 mm, Brownlee Labs, Inc., Santa Clara, CA).

Methods

Stock solutions of PYR were made at two concentrations for use in the preparation of the standard curve. Solution 1 contained 10 mg PYR/ml water and Solution 2 contained 1 mg PYR/ml water. Each solution was divided into 500-µl portions, placed in plastic microcentrifuge tubes and stored in the freezer. New stock solutions were made every month. Six concentrations of PYR in rodent chow were used for the standard curve and were prepared by adding various amounts of the stock solutions to rodent chow as shown in Table 1.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 1

Level	Target Conc. (mg PYR/g chow)	Chow (g)	Amt. of Stock Solution (µl)	Stock Solution #
1	2.00	1	200	1
2	1.00	1	100	1
3	0.50	1	50	1
4	0.10	1	100	2
5	0.05	1	50	2
6	0.01	2	20	2

A standard curve was run every day that analyses were performed.

Samples of the feed mixtures were extracted for analysis by adding water, shaking on a mechanical shaker, and centrifuging. The supernatant was poured into a volumetric flask, based on the concentration of sample as shown in Table 2.

Table 2

Dose Level (mg PYR/ g chow)	g of Diet Analyzed	ml of Water Added per Extraction	Minutes of Shaking per Extraction	Number of Extractions per Sample	Final Vol. (ml)
2.00	1	35	15	4	200
1.00	1	35	15	4	200
0.50	1	35	15	4	200
0.10	1	25	40	2	50
0.05	1	25	40	2	50
0.01	2	25	40	2	50

The volumetrics containing the combined extracts of each sample were brought to volume with water and mixed well.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Small portions of these solutions were filtered through 0.2 µm membrane filters directly into sample vials for subsequent HPLC analysis.

To determine the homogeneity of the feed mixtures, samples were taken from the left, right, and bottom ports of the Twin Shell Blender used in the preparation of the diet and analyzed in duplicate or triplicate for each dose level. Samples for testing homogeneity were collected during the first and thirteenth weeks of the study.

The analysis of PYR in the feed mixtures was accomplished under the following HPLC conditions:

Column: Brownlee silica 5 µm (100 x 4.6 mm)
Flow: 1.5 ml/min
Mobile Phase: 20% acetonitrile, 80% buffer
Buffer: 0.01 M heptanesulfonic acid
0.01 M sodium dihydrogen phosphate
0.0025 M tetramethylammonium chloride
pH adjusted to 3 with sulfuric acid
Wavelength Monitored: 269 nm
Injection Volume: 25 µl

Under these conditions, PYR eluted with a retention time of 2.5 minutes.

Calculations

All calculations were performed on either a TI 55-111 calculator or the HP-85 personal computer, which is part of the HP 1090 HPLC System. Results were in close agreement using either method. Least squares linear regression analysis of the standard concentration versus the peak height of PYR was performed to obtain the equation of the best fitting line in the form of

$$y = mx + b$$

where y is the peak height, m is the slope, x is the concentration (ng/µl), and b is the intercept. The concentration of each sample was calculated by substituting for y the peak height obtained by HPLC analysis and solving for x. To calculate the concentration of PYR in the diet in terms of mg PYR/g diet, the concentration of extract was multiplied by the dilution factor and divided by the weight of the diet sample extracted.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

$$\text{Concentration in diet} = \frac{\text{Conc. of extract x dilution factor}}{\text{Grams of diet extracted}}$$

When the calculations were performed on the 85 B personal computer, an average standard was entered into the program and the points on the standard curve run each day were averaged in with this curve. The resulting standard curve was used for calculating the values for that day's samples. Final concentrations of PYR in the diet were calculated on the 85 B by entering the proper dilution factor for each sample before the runs were made. All calculations were performed when the runs were integrated and the results were printed out on the chromatographic reports.

Initial intentions were to use the 85 B for all calculations since it was more convenient and less time consuming than the TI 55-111. However, due to either operator or instrumental error, results were not always obtained from the 85 B. In these instances, the TI 55-111 was used.

After the first month of the study, it was noted that the results for the lowest concentration dose were more consistent and accurate when a standard curve consisting of only the lowest three values of the daily standard curve was used. This curve was always calculated using the TI 55-111.

The plots of PYR concentration versus the peak height were linear within the range of concentrations analyzed. The results of the regression analysis for each run and the method of calculation are shown in Table 3.

Table 3: Regression Analysis Values for Each Run

Date of Run	y-intercept	Slope	Method of Calculation
5-Nov-86*	----	----	85 B
6-Nov-86	0.11991	0.06701	TI 55-111
7-Nov-86	-0.11140	0.07134	TI 55-111
10-Nov-86	-0.09979	0.07240	TI 55-111
12-Nov-86*	----	----	85 B
13-Nov-86	-0.13481	0.07124	TI 55-111

* These results were not printed out and saved.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 3 (cont.): Regression Analysis Values for Each Run

Date of Run	y-intercept	Slope	Method of Calculation
14-Nov-86	0.21714	0.06763	TI 55-111
17-Nov-86	-0.15374	0.07350	TI 55-111
18-Nov-86*	----	----	85 B
19-Nov-86	-0.02409	0.06918	TI 55-111
20-Nov-86	-0.02409	0.06918	TI 55-111
21-Nov-86	0.02978	0.06992	85 B
24-Nov-86	-0.10483	0.07487	85 B
25-Nov-86	-0.10483	0.07487	85 B
1-Dec-86	0.04999	0.06381**	85 B
2-Dec-86	-0.11485	0.06261	85 B
3-Dec-86	0.18716	0.05320	TI 55-111
3-Dec-86 (low conc)	-0.07324	0.05895	TI 55-111
4-Dec-86	-0.02315	0.06153	TI 55-111
4-Dec-86 (low conc)	-0.05328	0.06137	TI 55-111
10-Dec-86	0.04529	0.06122	85 B
11-Dec-86	-0.03430	0.06159	85 B
12-Dec-86	-0.03430	0.06160	85 B
17-Dec-86	0.04519	0.06360	85 B
18-Dec-86	0.06507	0.06427	85 B
5-Jan-87	0.09999	0.06428	85 B
6-Jan-87	0.04261	0.06681	85 B
6-Jan-87 (low conc)	-0.02199	0.06834	TI 55-111
7-Jan-87	0.03631	0.06719	85 B
7-Jan-87 (low conc)	0.08869	0.07162	TI 55-111
9-Jan-87	0.04124	0.06607	85 B
9-Jan-87 (low conc)	-0.06343	0.06929	TI 55-111
12-Jan-87	0.03472	0.06506	85 B
13-Jan-87	0.05315	0.06639	85 B
14-Jan-87	-0.02611	0.06859	85 B
15-Jan-87	-0.03996	0.06839	85 B
20-Jan-87	0.00972	0.06744	85 B
21-Jan-87	-0.03440	0.06749	85 B
22-Jan-87	-0.00037	0.06749	85 B
27-Jan-87	-0.01826	0.06223**	85 B
28-Jan-87	-0.01548	0.06419	TI 55-111
29-Jan-87	-0.10175	0.06136	85 B
2-Feb-87	-0.00757	0.06179	85 B

* These results were not printed out and saved.
** The column went dry and affected the slope of the standard curve.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 3 (cont.): Regression Analysis Values for Each Run

Date of Run	y-intercept	Slope	Method of Calculation
3-Feb-87	-0.00757	0.06179	85 B
3-Feb-87 (low conc)	-0.03661	0.06215	TI 55-111
4-Feb-87	-0.04286	0.06288	85 B
5-Feb-87	-0.03285	0.06224	85 B
9-Feb-87	-0.01013	0.06192	85 B
9-Feb-87 (low conc)	-0.09660	0.06329	TI 55-111
11-Feb-87	-0.02811	0.06218	85 B
11-Feb-87 (low conc)	-0.07611	0.06165	TI 55-111
12-Feb-87	-0.02435	0.06189	85 B
12-Feb-87 (low conc)	-0.06025	0.06128	TI 55-111
18-Feb-87	-0.01429	0.06154	85 B
18-Feb-87 (low conc)	-0.06049	0.06064	TI 55-111
19-Feb-87	-0.08454	0.06434	85 B
25-Feb-87	0.09787	0.05144*	85 B
25-Feb-87 (low conc)	-0.06000	0.05496	TI 55-111
26-Feb-87	-0.05239	0.04827	85 B
4-Mar-87	0.02750	0.05762	85 B
5-Mar-87	0.00086	0.05842	85 B
11-Mar-87	0.05947	0.05599	85 B
12-Mar-87	0.00224	0.05686	85 B
18-Mar-87	0.03156	0.05721	85 B
18-Mar-87 (low conc)	-0.03014	0.05723	TI 55-111
25-Mar-87	-0.00694	0.05624	85 B
25-Mar-87 (low conc)	0.03689	0.05099	TI 55-111
1-Apr-87	0.00634	0.05629	85 B
8-Apr-87	-0.02953	0.05749	85 B
8-Apr-87 (low conc)	0.03247	0.05749	TI 55-111
21-Apr-87	0.02658	0.06218	85 B
22-Apr-87	-0.03619	0.05784	85 B
5-May-87	-0.01189	0.05723	85 B
11-May-87	-0.06157	0.05754	85 B
11-May-87 (low conc)	-0.07033	0.05509	TI 55-111

* The column was replaced with a new one.

The results from the analysis of the diet mixtures are shown in Table 4.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 4

Group/ Sex	Study Week	Target Conc.*	Batch Number	Date Prepared	Date Analyzed	Conc. Determined by Analysis	% of Target Conc.
2/M	1	0.0114	1	4-Nov-86	5-Nov-86	0.0122	107.0
3/M	1	0.1064	1	4-Nov-86	10-Nov-86	0.0972	91.4
3/M	1	0.1064	2	4-Nov-86	10-Nov-86	0.0989	93.0
4/M	1	0.3260	1	4-Nov-86	10-Nov-86	0.3150	96.6
4/M	1	0.3260	2	4-Nov-86	10-Nov-86	0.3180	97.5
5/M	1	0.6339	1	4-Nov-86	6-Nov-86	0.6153	97.1
6/M	1	1.0099	1	4-Nov-86	6-Nov-86	1.0447	103.4
2/M	2	0.0124	1	11-Nov-86	17-Nov-86	0.0127	102.4
2/M	2	0.0124	2	11-Nov-86	17-Nov-86	0.0131	105.6
3/M	2	0.1190	1	11-Nov-86	13-Nov-86	0.1092	91.8
3/M	2	0.1190	2	11-Nov-86	17-Nov-86	0.1109	93.2
4/M	2	0.3590	1	11-Nov-86	17-Nov-86	0.3677	102.5
4/M	2	0.3590	2	11-Nov-86	17-Nov-86	0.3487	97.1
5/M	2	0.7470	1	11-Nov-86	13-Nov-86	0.7330	98.1
6/M	2	1.4330	1	11-Nov-86	13-Nov-86	1.3510	94.3
2/M	3	0.0135	1	18-Nov-86	25-Nov-86	0.0122	90.4
2/M	3	0.0135	2	18-Nov-86	25-Nov-86	0.0126	93.3
3/M	3	0.1340	1	18-Nov-86	19-Nov-86	0.1220	91.0
3/M	3	0.1340	2	18-Nov-86	19-Nov-86	0.1180	88.1
4/M	3	0.3990	1	18-Nov-86	19-Nov-86	0.3860	96.7
4/M	3	0.3990	2	18-Nov-86	19-Nov-86	0.3710	93.0
5/M	3	0.7595	1	18-Nov-86	21-Nov-86	0.7163	94.3
6/M	3	1.2203	1	18-Nov-86	21-Nov-86	1.1000	90.1
2/M	4	0.0150	1	25-Nov-86	2-Dec-86	0.0138	92.0
2/M	4	0.0150	2	25-Nov-86	2-Dec-86	0.0138	92.0
3/M	4	0.1470	1	25-Nov-86	2-Dec-86	0.1330	90.5
3/M	4	0.1470	2	25-Nov-86	2-Dec-86	0.1360	92.5
4/M	4	0.4400	1	25-Nov-86	2-Dec-86	0.4120	93.6
4/M	4	0.4400	2	25-Nov-86	2-Dec-86	0.4100	93.2
5/M	4	0.8460	1	25-Nov-86	1-Dec-86	0.7870	93.0
6/M	4	1.2610	1	25-Nov-86	1-Dec-86	1.1620	92.1
2/M	5	0.0158	1	2-Dec-86	3-Dec-86	0.0146	92.4
2/M	5	0.0158	2	2-Dec-86	3-Dec-86	0.0144	91.1
3/M	5	0.1520	1	2-Dec-86	4-Dec-86	0.1370	90.1
3/M	5	0.1520	2	2-Dec-86	4-Dec-86	0.1320	86.8
4/M	5	0.4620	1	2-Dec-86	4-Dec-86	0.4130	89.4
4/M	5	0.4620	2	2-Dec-86	4-Dec-86	0.4240	91.8

* mg PYR/g chow.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 4 (cont.)

Group/ Sex	Study Week	Target Conc.*	Batch Number	Date Prepared	Date Analyzed	Conc. Determined by Analysis	% of Target Conc.
5/M	5	0.8840	1	2-Dec-86	3-Dec-86	0.8820	99.8
6/M	5	1.2870	1	2-Dec-86	4-Dec-86	1.1410	88.7
2/M	6	0.0172	1	9-Dec-86	10-Dec-86	0.0185	107.6
2/M	6	0.0172	2	9-Dec-86	10-Dec-86	0.0177	102.9
3/M	6	0.1702	1	9-Dec-86	12-Dec-86	0.1677	98.5
3/M	6	0.1702	2	9-Dec-86	12-Dec-86	0.1756	103.2
4/M	6	0.5129	1	9-Dec-86	12-Dec-86	0.5351	104.3
5/M	6	0.9769	1	9-Dec-86	12-Dec-86	0.9762	99.9
6/M	6	1.4170	1	9-Dec-86	10-Dec-86	1.5680	110.7
2/F	1	0.0117	1	10-Dec-86	11-Dec-86	0.0117	100.0
3/F	1	0.1127	1	10-Dec-86	11-Dec-86	0.1167	103.5
4/F	1	0.3165	1	10-Dec-86	11-Dec-86	0.3483	110.0
5/F	1	0.6925	1	10-Dec-86	11-Dec-86	0.6626	95.7
6/F	1	1.0542	1	10-Dec-86	11-Dec-86	1.0889	103.3
2/M	7	0.0183	1	16-Dec-86	9-Jan-87	0.0180	98.4
2/M	7	0.0183	2	16-Dec-86	9-Jan-87	0.0165	90.2
3/M	7	0.1763	1	16-Dec-86	17-Dec-86	0.1843	104.5
3/M	7	0.1763	2	16-Dec-86	17-Dec-86	0.1869	106.0
4/M	7	0.5160	1	16-Dec-86	17-Dec-86	0.4852	94.0
5/M	7	1.0377	1	16-Dec-86	17-Dec-86	1.0989	105.9
6/M	7	1.5221	1	16-Dec-86	17-Dec-86	1.5240	100.1
2/F	2	0.0123	1	17-Dec-86	9-Jan-87	0.0114	92.7
3/F	2	0.1179	1	17-Dec-86	18-Dec-86	0.1163	98.6
4/F	2	0.3480	1	17-Dec-86	18-Dec-86	0.3560	102.3
5/F	2	0.7678	1	17-Dec-86	18-Dec-86	0.7849	102.2
6/F	2	1.3770	1	17-Dec-86	18-Dec-86	1.4760	107.2
2/M	8	0.0180	1	23-Dec-86	9-Jan-87	0.0156	86.7
2/M	8	0.0180	2	23-Dec-86	9-Jan-87	0.0163	90.6
3/M	8	0.1841	1	23-Dec-86	9-Jan-87	0.1759	95.5
3/M	8	0.1841	2	23-Dec-86	9-Jan-87	0.1809	98.3
4/M	8	0.5351	1	23-Dec-86	9-Jan-87	0.3202	59.8@
5/M	8	1.1079	1	23-Dec-86	5-Jan-87	1.1147	100.6
6/M	8	1.6033	1	23-Dec-86	5-Jan-87	1.6736	104.4
2/F	3	0.0134	1	24-Dec-86	6-Jan-87	0.0123	91.8
3/F	3	0.1240	1	24-Dec-86	6-Jan-87	0.1215	98.0
4/F	3	0.3725	1	24-Dec-86	6-Jan-87	0.3687	99.0

* mg PYR/g chow.
@ This sample was misprepared.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 4 (cont.)

Group/ Sex	Study Week	Target Conc.*	Batch Number	Date Prepared	Date Analyzed	Conc. Determined by Analysis	% of Target Conc.
5/F	3	0.7770	1	24-Dec-86	6-Jan-87	0.7665	98.6
6/F	3	1.1926	1	24-Dec-86	6-Jan-87	1.2393	103.9
2/M	9	0.0188	1	30-Dec-86	12-Jan-87	0.0171	91.0
2/M	9	0.0188	2	30-Dec-86	12-Jan-87	0.0166	88.3
3/M	9	0.1831	1	30-Dec-86	7-Jan-87	0.1781	97.3
3/M	9	0.1331	2	30-Dec-86	7-Jan-87	0.1768	96.6
4/M	9	0.5386	1	30-Dec-86	7-Jan-87	0.5255	97.6
5/M	9	1.1137	1	30-Dec-86	7-Jan-87	1.1006	98.8
6/M	9	1.5434	1	30-Dec-86	7-Jan-87	1.5495	100.4
2/F	4	0.0139	1	31-Dec-86	12-Jan-87	0.0124	89.2
3/F	4	0.1376	1	31-Dec-86	12-Jan-87	0.1324	96.2
4/F	4	0.4126	1	31-Dec-86	12-Jan-87	0.4123	99.9
5/F	4	0.8325	1	31-Dec-86	12-Jan-87	0.8329	100.0
6/F	4	1.2055	1	31-Dec-86	12-Jan-87	1.1626	96.4
2/M	10	0.0199	1	6-Jan-87	14-Jan-87	0.0180	90.5
2/M	10	0.0199	2	6-Jan-87	14-Jan-87	0.0172	86.4
3/M	10	0.1939	1	6-Jan-87	13-Jan-87	0.1778	91.7
3/M	10	0.1939	2	6-Jan-87	13-Jan-87	0.1838	94.8
4/M	10	0.5616	1	6-Jan-87	13-Jan-87	0.5510	98.1
5/M	10	1.1395	1	6-Jan-87	13-Jan-87	1.0771	94.5
6/M	10	1.7373	1	6-Jan-87	13-Jan-87	1.6859	97.0
2/F	5	0.0155	1	7-Jan-87	14-Jan-87	0.0155	100.0
3/F	5	0.1444	1	7-Jan-87	14-Jan-87	0.1409	97.6
4/F	5	0.4344	1	7-Jan-87	14-Jan-87	0.3999	92.1
5/F	5	0.9521	1	7-Jan-87	14-Jan-87	0.9038	94.9
6/F	5	1.2662	1	7-Jan-87	14-Jan-87	1.2310	97.2
2/M	11	0.0200	1	13-Jan-87	20-Jan-87	0.0182	91.0
2/M	11	0.0200	2	13-Jan-87	20-Jan-87	0.0194	97.0
3/M	11	0.2005	1	13-Jan-87	15-Jan-87	0.1930	96.3
3/M	11	0.2005	2	13-Jan-87	15-Jan-87	0.1969	98.2
4/M	11	0.5532	1	13-Jan-87	15-Jan-87	0.5288	95.6
5/M	11	1.2287	1	13-Jan-87	15-Jan-87	1.2685	103.2
6/M	11	1.7356	1	13-Jan-87	15-Jan-87	1.6904	97.4
2/F	6	0.0147	1	14-Jan-87	20-Jan-87	0.0125	85.0
3/F	6	0.1483	1	14-Jan-87	20-Jan-87	0.1557	105.0
4/F	6	0.4410	1	14-Jan-87	20-Jan-87	0.4354	98.7
5/F	6	0.9293	1	14-Jan-87	20-Jan-87	0.9418	101.3

* mg PYR/g chow.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 4 (cont.)

Group/ Sex	Study Week	Target Conc.*	Batch Number	Date Prepared	Date Analyzed	Conc. Determined by Analysis	% of Target Conc.
6/F	6	1.3230	1	14-Jan-87	20-Jan-87	1.2889	97.4
2/M	12	0.0215	1	20-Jan-87	22-Jan-87	0.0188	87.4
2/M	12	0.0215	2	20-Jan-87	22-Jan-87	0.0185	86.0
3/M	12	0.2045	1	20-Jan-87	21-Jan-87	0.1976	96.6
3/M	12	0.2045	2	20-Jan-87	21-Jan-87	0.2055	100.5
4/M	12	0.6292	1	20-Jan-87	21-Jan-87	0.6333	100.7
5/M	12	1.2612	1	20-Jan-87	21-Jan-87	1.2740	101.0
6/M	12	1.8150	1	20-Jan-87	21-Jan-87	1.8737	103.2
2/F	7	0.0157	1	21-Jan-87	26-Jan-87	0.0142	90.4
3/F	7	0.1648	1	21-Jan-87	22-Jan-87	0.1541	93.5
4/F	7	0.4669	1	21-Jan-87	22-Jan-87	0.4458	95.5
5/F	7	0.9876	1	21-Jan-87	22-Jan-87	0.9656	97.8
6/F	7	1.3706	1	21-Jan-87	23-Jan-87	1.3503	98.5
2/M	13	0.0237	1	27-Jan-87	29-Jan-87	0.0227	95.8
2/M	13	0.0237	2	27-Jan-87	29-Jan-87	0.0225	94.9
3/M	13	0.2208	1	27-Jan-87	2-Feb-87	0.2183	98.9
3/M	13	0.2208	2	27-Jan-87	2-Feb-87	0.2182	98.8
4/M	13	0.6722	1	27-Jan-87	28-Jan-87	0.6550	97.4
5/M	13	1.3443	1	27-Jan-87	29-Jan-87	1.4118	105.0
6/M	13	2.5908	1	27-Jan-87	2-Feb-87	2.7393	105.7
2/F	8	0.0159	1	28-Jan-87	3-Feb-87	0.0143	89.9
3/F	8	0.1585	1	28-Jan-87	3-Feb-87	0.1558	98.3
4/F	8	0.4538	1	28-Jan-87	3-Feb-87	0.4669	102.9
5/F	8	1.0582	1	28-Jan-87	4-Feb-87	1.0610	100.3
6/F	8	1.3981	1	28-Jan-87	4-Feb-87	1.4149	101.2
2/M	14	0.0229	1	3-Feb-87	4-Feb-87	0.0204	89.1
3/M	14	0.2183	1	3-Feb-87	5-Feb-87	0.2096	96.0
3/M	14	0.2183	2	3-Feb-87	5-Feb-87	0.2023	92.7
4/M	14	0.6800	1	3-Feb-87	5-Feb-87	0.6770	99.6
5/M	14	1.3756	1	3-Feb-87	5-Feb-87	1.3501	98.1
6/M	14	1.9451	1	3-Feb-87	5-Feb-87	1.8748	96.4
2/F	9	0.0170	1	4-Feb-87	9-Feb-87	0.0155	91.2
3/F	9	0.1613	1	4-Feb-87	9-Feb-87	0.1539	95.4
4/F	9	0.4808	1	4-Feb-87	9-Feb-87	0.4807	100.0
5/F	9	1.0726	1	4-Feb-87	9-Feb-87	1.1012	102.7
6/F	9	1.5170	1	4-Feb-87	9-Feb-87	1.5767	103.9
2/F	10	0.0173	1	11-Feb-87	12-Feb-87	0.0157	90.8

* mg PYR/g chow.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 4 (cont.)

Group/ Sex	Study Week	Target Conc.*	Batch Number	Date Prepared	Date Analyzed	Conc. Determined by Analysis	% of Target Conc.
3/F	10	0.1780	1	11-Feb-87	12-Feb-87	0.1717	96.5
4/F	10	0.5012	1	11-Feb-87	12-Feb-87	0.5146	102.7
5/F	10	1.1047	1	11-Feb-87	12-Feb-87	1.1554	104.6
6/F	10	1.5811	1	11-Feb-87	12-Feb-87	1.6181	102.3
2/F	11	0.0181	1	18-Feb-87	19-Feb-87	0.0174	96.1
3/F	11	0.1822	1	18-Feb-87	19-Feb-87	0.1830	100.4
4/F	11	0.5229	1	18-Feb-87	19-Feb-87	0.5275	100.9
5/F	11	1.1537	1	18-Feb-87	19-Feb-87	1.1742	101.8
6/F	11	1.8954	1	18-Feb-87	19-Feb-87	1.9432	102.5
2/F	12	0.0239	1	25-Feb-87	26-Feb-87	0.0237	99.2
3/F	12	0.2186	1	25-Feb-87	26-Feb-87	0.2159	98.8
4/F	12	0.5751	1	25-Feb-87	26-Feb-87	0.6168	107.3
5/F	12	1.2716	1	25-Feb-87	26-Feb-87	1.3129	103.2
6/F	12	1.7411	1	25-Feb-87	26-Feb-87	1.8597	106.8
2/F	13	0.0186	1	4-Mar-87	5-Mar-87	0.0162	87.1
3/F	13	0.1843	1	4-Mar-87	5-Mar-87	0.1841	99.9
4/F	13	0.5319	1	4-Mar-87	5-Mar-87	0.5302	99.7
5/F	13	1.1575	1	4-Mar-87	5-Mar-87	1.1687	101.0
6/F	13	1.6050	1	4-Mar-87	5-Mar-87	1.7029	106.1
4/F	14	0.5551	1	11-Mar-87	12-Mar-87	0.5534	99.7
5/F	14	1.1195	1	11-Mar-87	12-Mar-87	1.1803	105.4

* mg PYR/g chow.

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Results of the homogeneity study are presented in Tables 5, 6, and 7.

Table 5

Target Conc. of PYR (mg/g)	Site of Sampling	Conc. Detn. by Analysis (mg/g)	Mean Conc. (mg/g)	Absolute Deviation from Mean (%)
		Week 1 - Males		
	Right	0.01208		0.8
0.0114	Left	0.01220	0.01218	0.2
	Bottom	0.01225		0.6
	Right	0.09357		2.5
0.1070	Left	0.09537	0.09596	0.6
	Bottom	0.09893		3.1
	Right	0.3256		3.4
0.3260	Left	0.3046	0.3149	3.3
	Bottom	0.3145		0.1
	Right	0.6140		0.2
0.6339	Left	0.6272	0.6153	1.9
	Bottom	0.6048		1.7
	Right	1.0461		5.4
1.0099	Left	1.0136	0.9927	2.1
	Bottom	0.9185		7.5

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 6

Target Conc. of PYR (mg/g)	Site of Sampling	Conc. Detn. by Analysis (mg/g)	Mean Conc. (mg/g)	Absolute Deviation from Mean (%)
		Week 13 - Males		
	Right	0.0227		1.2
0.0237	Left	0.0227	0.0224	1.2
	Bottom	0.0219		2.4
	Right	0.2292		1.6
0.2375	Left	0.2286	0.2255	1.4
	Bottom	0.2187		3.0
	Right	0.2183		0.1
0.2208	Left	0.2234	0.2185	2.2
	Bottom	0.2138		2.2
	Right	0.6519		0.5
0.6722	Left	0.6643	0.6550	1.4
	Bottom	0.6489		0.9
	Right	1.3841		1.7
1.3443	Left	1.4261	1.4073	1.3
	Bottom	1.4118		0.3
	Right	2.7393		0.1
2.5908	Left	2.7495	2.7413	0.3
	Bottom	2.7352		0.2

Appendix F (cont.): ANALYSIS OF FEED MIXTURES

Table 7

Target Conc. of PYR (mg/g)	Site of Sampling	Conc. Detn. by Analysis (mg/g)	Mean Conc. (mg/g)	Absolute Deviation from Mean (%)
		Week 13 - Females		
	Right	0.0141		1.2
0.0159	Left	0.0145	0.0143	1.6
	Bottom	0.0142		0.5
	Right	0.1563		0.3
0.1585	Left	0.1560	0.1558	0.1
	Bottom	0.1551		0.4
	Right	0.4930		5.6
0.4538	Left	0.4431	0.4669	5.1
	Bottom	0.4647		0.5
	Right	1.0253		3.4
1.0582	Left	1.0846	1.0610	2.2
	Bottom	1.0730		1.1
	Right	1.4140		0.1
1.3981	Left	1.4656	1.4149	3.6
	Bottom	1.3652		3.5

Discussion

The concentration of PYR in the mixtures was within 10% of the target concentration with the exception of 10% of the diet mixture samples, which were within 15% of the target concentration. One sample was misprepared and was 40% low. Samples collected during the first and thirteenth weeks of the study showed that the PYR concentrations were homogeneous in the feed over the range tested, according to the EPA and NIH criteria for homogeneity[1].

[1] EPA, GLP Standards, Final Rule (40 CFR 160) as published in the Federal Register, Vol. 48, n.1. 230, Nov 29, 1983, p. 53955-53959.

Appendix G: PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

Title: AutoAnalyzer II Procedure for the Determination of Erythrocyte Acetylcholinesterase and Plasma Cholinesterase Activities in Pyridostigmine - Inhibited Blood.

Scope: This SOP specifies the instrumentation, reagents, and procedures used to measure cholinesterase activities in animal blood derived from investigations which involve the use of pyridostigmine or similar anti-cholinesterase compounds.

References:

1. FDA GLP regulations (21 CFR58) and preamble as published in the Federal Register, 22 Aug 78 (43 FR 5986-60025).

2. EPA GLP regulations (40 CFR792) and preamble as published in the Federal Register, 29 Nov 83 (48 FR 53922).

3. Kaminskis, A., "Determination of Erythrocyte Acetylcholinesterase Activity in Pyridostigmine Inhibited Human Blood." SOP Analytical Chemistry Branch, US Army Medical Research Institute for Chemical Defense, 18 Jun 85.

4. Ellman, G.L., K.D. Courtney, V. Andres, Jr. and R.M. Featherstone. "A New and Rapid Colorimetric Determination of Acetylcholinesterase Activity." Biochem. Pharm. 7:88-95, 1961.

5. Humiston, C.G. and G.J. Wright. "An Automated Method for the Determination of Cholinesterase Activity." Toxicology and Applied Pharm. 10:467-480, 1967.

6. Groff, W.A., A. Kaminskis and R.I. Ellin. "Interconversion of Cholinesterase Enzyme Activity Units by the Manual Delta pH Method and a Recommended Automated Method." Clin Tox.. 9:353-358, 1976.

7. Technical Publication No. TG1-0170-01, "Course Guide for the Technicon AutoAnalyzer II System." Technicon Instruments Corp., Tarrytown, New York, Aug 72.

8. Technicon Manual No. TP1-0170-10, "Programmed Instruction for the Technicon AutoAnalyzer II System." Technicon Instruments Corp., Tarrytown, New York, Dec 73.

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

9. Meyer, S.L. Straight-line Graphs and Fitting. In: Data Analysis for Scientists and Engineers. John Wiley & sons, Inc., New York, NY, 1975, pp 71-75.

Purpose: To apply the essential requirements of an accepted method for measuring cholinesterase activity in human blood (3) in performing comparable measurements using animal blood.

Justification for Reference Method Modifications

Species differences in erythrocyte and plasma cholinesterase activities prohibit direct utilization of previously reported methods without some modification. To establish comparability of values between human and animal blood, the reference method was modified to increase measurement sensitivity at lower activity levels and to compensate for species variability in hemolytic susceptibility. The basic reaction mechanism and underlying measurement principles were not changed. A list of hardware and procedural differences is included in Appendix A.

Method Derivation and Reaction Mechanism

This SOP was adapted from the AutoAnalyzer procedure of Kaminskis for measuring acetylcholinesterase activity in human erythrocytes (3). His method was based on the basic reaction mechanism of Ellman's manual assay (4) as previously modified for semi-automated continuous flow analyses (5,6).

In the presence of nonlimiting amounts of acetylthiocholine substrate under controlled reaction conditions, red cell acetylcholinesterase (E.C. 3.1.1.7) and plasma cholinesterase (E.C. 3.1.1.8) catalyze the production of thiocholine and acetic acid at rates proportionate to enzyme concentration. Thiocholine reacts with DTNB, 5,5'-dithiobis-(2-nitrobenzoic acid), to produce equimolar amounts of a mixed disulfide and colored dianion, 2-nitro-5-thiobenzoic acid. The absorbance change at 410 nm occurring within a measured time period is proportionate to enzymatic activity when properly blanked and calibrated.

Equipment and Materials

A. Instruments

1. AutoAnalyzer II System consisting of a Technicon Sampler IV, Proportioning Pump III, Two Channel Recorder, two Single

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

Channel Colorimeters with 15 mm flow cells and 410 nm filters, and two identical Cholinesterase Chemistry Modules constructed according to the manifold diagram shown in Fig. 1 using the hardware components listed in Appendix A.

2. Eppendorf Micro-Centrifuge Model 5412.

3. Beckman Altex PHI 61 pH meter.

B. **Miscellaneous Equipment**

1. Analytical balance

2. Eppendorf and Gilsen pipettors and disposable tips

3. 1.5 mL polypropylene centrifuge tubes

4. 2.5 mL AutoAnalyzer cups

5. 0-100 linear chart scale paper

C. Chemicals

Chemical Name	Supplier's Address	Catalog #
Tris (hydroxymethyl) aminomethane	Sigma Chemical Co St Louis, MO	T-1503
5,5'-dithiobis (2-nitrobenzoic acid)	. . . . .	D-8130
Brij 35,30% solution	. . . . .	430 AG-6
Acetylthiocholine iodide	. . . . .	A-5751
Reduced Glutathione	. . . . .	G-4251
Eel Acetylcholinesterase, Type VI-S	. . . . .	C-3389
Bovine Albumin, Fx V	. . . . .	A-4503
Hydrochloric Acid	JT Baker Chemicals Co Phillipsburg, NJ	9530-3
Sodium Chloride (NaCl)AR	. . . . .	5-3624
Ethylenedinitrilo-tetraacetic acid (EDTA) disodium dihydrate	Mallinchrodt Chemical Works, St. Louis, MO	4931

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

AutoAnalyzer System Mechanisms

The system Flow Diagram is shown in Figure 1. Sampled specimens are split into two equal aliquots which are injected into separate but identical flow pathways. One path combines DTNB reagent (Tris-buffered at pH 8.2) with specimen and acetylthiocholine in saline (Channel A). The second substitutes saline without substrate in an otherwise identical blanking reaction mixture (Channel B). Both streams are incubated in 37° C heating baths before passage through 24 inch dialyzers.

Dialysates in Tris buffer are mixed and debubbled prior to passage through the flow cells of two colorimeters. A 30/hr, 1:2 (sample: wash) cam in the Sampler IV provides acceptable flow cell flushing for baseline recovery between peaks.

Procedures

Preparation of Reagents

1) **AutoAnalyzer Wash Solution:**

Add 1.5 mL of Brij 35, 30% solution to 1 L of distilled deionized water (DD). Mix thoroughly with magnetic stirrer.

2) **50 mM Tris Buffer, pH 8.2, containing 114 mM NaCl:**

Dissolve 6.05 g Tris base and 6.64 g NaCl in 900 mL DD-water. Adjust pH to 8.2 by drop wise addition of con HCL. Dilute to 1L with DD water and add 1.5 mL of Brij 35. Confirm pH after thorough mixing and readjust if necessary.

3) **1.68 mM DTNB reagent:**

Dissolve 0.6653 g DTNB in 1 L of 50 mM Tris buffer, pH 8.2 (see above). Mix with magnetic stirrer until clear, yellow solution. Confirm pH 8.2 and adjust if necessary.

4) **0.9% NaCl:**

Dissolve 9 g NaCl in 900 mL DD water and dilute to 1 L with DD water.

5) **1mM EDTA:**

Dissolve 0.372 g EDTA-disodium dihydrate salt in 1 L DD water.

6) **12.7 mM Acetylthiocholine (ATC) Substrate:**

Prepare 100 mM ATC by dissolving 1.4478g of acetylthiocholine iodide in 50 mL of 0.9% saline. Dilute 12.7 mL of 100 mM ATC to 100 mL using 0.9% saline.

Preparation of Standards and Controls

1) **60 mM Reduced Glutathione (GSH) Stock Standard:**

Dissolve 0.9219 g GSH in 40 mL of 1 mM EDTA. Dilute to 50 mL with 1 mM EDTA. Store in refrigerator in separate 1 mL aliquots in tightly capped vials. Stock preparation is stable up to 6 months at refrigerator temperature.

2) **Working GSH Standard Dilutions:**

On day of assay, warm an aliquot of 60 mM GSH stock standard. Add 0.2 mL of stock to 9.8 mL of 1 mM EDTA, and mix on vortex. Prepare standard dilutions according to the following table:

Lab #	Aliquot 60 mM GSH (mL)	+	Aliquot 1 mM EDTA (mL)	Concentration (umol GSH/mL)
S0	0		2.00	0
S1	0.25		1.75	0.15
S2	0.50		1.50	0.30
S3	1.00		1.00	0.60
S4	1.50		0.50	0.90
S5	2.00		0	1.20
S6	2.00		0	1.20

Prepare fresh dilutions for each day's assays and confirm concentrations using a spectrophotometric assay.

3) **Stock Eel Acetylcholinesterase Control:**

Dissolve 1 g Serum Bovine Albumin in 100 mL of 0.9% NaCl. Use 50 mL of this diluent to dissolve 1.7 mg of Eel Cholinesterase lyophilized powder. Store frozen in 1 mL aliquots in capped polypropylene tubes.

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

4) Working Eel Acetylcholinesterase control dilutions:

On day of assay, thaw an aliquot of stock control, and warm to room temperature. Prepare dilutions according to the following table:

Lab #	Aliquot stock control (mL)	+	aliquot saline diluent (mL)
E1	0.025		1.975
E2	0.050		1.950
E3	0.075		1.925
E4	0.100		1.900

Prepare fresh dilutions for each day's assays and include analyses of all dilutions in the beginning and end of each day's run.

Preparation of Blood Specimens

1) Use freshly drawn whole blood anticoagulated with EDTA.

2) Transfer aliquots into capillary tubes for duplicate Micro-hematocrit determinations on each specimen.

3) Transfer measured volumes of whole blood into 1.5 mL polypropylene centrifuge tubes labelled to identify specimens in the sample preparations shown below.

4) Centrifuge at 15000 RPM in Eppendorf centrifuge for 2 min.

5) Withdraw plasma as completely as possible without disturbing the packed red cells (PCV) and transfer plasma into I.D. labelled tubes.

6) Select one or more of the following options for red blood cell preparation:

a. Unwashed intact red cells - Add 1 mL 0.9% saline to PCV, gently mix to complete and uniform suspension, and transfer to AAII cups for immediate sampling.

b. **Washed intact red cells** - Perform saline suspension as for "unwashed" cells but remove and discard supernatants after 1 min centrifugation. Repeat twice before transferring final suspension into AAII cups for immediate sampling.

c. **Unwashed hemolyzed red cells** - Add measured volume of specified lysing solution (max 1.5 mL) to PCV after plasma removal. Mix on vortex mixer for 30 sec. Transfer to AAII cups for sampling.

d. **Washed hemolyzed red cells** - Perform saline washes as for "washed intact red cells" and discard supernatant after final wash. Continue preparation as for "unwashed hemolyzed red cells." Transfer to AAII cups for sampling.

7) Add measured volume of plasma from each specimen into a specified volume of 0.9% saline in identification labelled AAII cups and mix thoroughly before sampling by system.

8) Record sample preparation designation codes and note any exceptions for individual specimens for subsequent calculation of dilution factors.

Operation and Maintenance of AutoAnalyzer II System

1) Perform general maintenance operations as outlined in LAIR OP-ACH-26 except use Brij 35/water flushing solution.

2) Install or confirm correct chemistry module and pump tube manifold for assay shown in Flow Diagram of Figure 1.

3) Turn on power to all instrument modules for minimum 30 min warm up.

4) Engage pump tubes, insert platen and initiate flush of flow system using freshly prepared Brij 35/H_2O wash solution during warm up period. Observe bubble pattern for regularity of size and flow. Initiate corrective action according to OP-ACH-26 if required.

5) After stabilization of electronic components, check alignment of colorimeter signal ouputs with recorder scale. Use screwdriver adjustments on colorimeter as necessary: Display rotary switch position zero, recorder baseline, zero. Display rotary switch position full scale, recorder pen deflection full scale (100 chart units).

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

6) Set baseline controls to rotation midpoint (5 turns from either limit), all apertures fully open (aperture knurled screws rotated fully clockwise), and Std Cal controls of both channels to 350.

7) Initiate flow of reagents in pump tubes as shown in Figure 1. After 15 min, turn rotary display switches to position Normal on both colorimeters.

8) Set recorder pen positions for baseline (0 chart units) by adjusting reference apertures on both colorimeters. Use baseline controls for fine tuning.

Assay Calibration (7,8)

1) Activate Sampler to initiate sampling of GSH Std dilutions in the following sequence:

(1) 1.2 umol GSH/mL
(2) 1 mM EDTA blank
(3) 0.15 umol GSH/mL
(4) 0.30 " "
(5) 0.60 " "
(6) 0.90 " "
(7) 1.20 " "
(8) 1 mM EDTA blank.

2) Measure and record the reaction time in minutes from the point of substrate injection into the stream flow to dialyzer exit. (Additional air bubbles drawn into the stream during sampler probe movement from reservoir to sample cup and the color intensity of the highest GSH std can be used to perform this measurement accurately and reproducibly.) Reaction time approximates 3.9 min with the chemistry module components and pump tubes shown in Figure 1 and listed in Appendix A.

3) As the peak corresponding with the highest GSH std in the presence of ATC substrate is recorded, adjust the STD Cal control of the channel without substrate to achieve equivalent pen deflection. Record the control settings.

4) Observe peaks for succeeding series of GSH Std dilutions and repeat calibration procedure if equivalent response in the presence or absence of substrate is not confirmed throughout the std concentration range.

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

5) Set rotary display switches of both colorimeters to DARK 1 position after acceptable calibration.

6) Assay a series of eel acetylcholinesterase Control dilutions immediately following a complete set of GSH Stds prior to and on completion of a designated group of specimen analyses.

7) Use GSH stds as markers during extended runs to confirm calibration stability and aid in peak identification.

Specimen Analyses

1) Initiate sampling of specimen preparations in a recorded sequence to enable peak identification on the chart record.

2) Repeat analysis of specimens exhibiting overscale chart peaks using appropriate dilutions of the cup preparation. Specify corrective action on the chart record at associated peak.

3) Repeat sampling of cup preparations whose peaks follow abnormal baseline elevations with insertion of a preceding wash cup (Brij/H_2O).

4) Annotate the chart record to identify the study, assay, specimens, data, instrument operation variables, and date of run.

5) Sign chart record which comprises the primary raw data of the assay.

6) Flush entire flow system using Brij/H_2O wash solution for a minimum of 30 min before shutdown.

7) Turn off power, release platen, and disengage pump tubes.

Data Processing

1) Measure peak heights on the chart record as the difference in the number of chart units (C.U.) between the baseline value immediately before each peak and the point of maximum pen deflection. (A transparent overlay transcribed with 0-100 divisions equivalent to those of the chart scale facilitates these measurements.)

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

2) Record C.U. values with corresponding identification numbers on Data Worksheets for subsequent calculation and evaluation procedures.

3) Record all other pertinent information and variables required for identification, calculations, results, and assay quality control.

4) Perform calculations as subsequently indicated in SOP and record results in format shown in Figures 2-5.

5) Assure compliance with requirements of Good Laboratory Practices (GLP) in maintenance and disposition of records and data.

Calculations

1) Calculate linear regression for GSH standard by the Method of Least Squares (9) expressed as ($y = mx + b$). Determine the correlation coefficient (r).

2) Use regression to calculate concentration values corresponding to peak heights of specimen and control cup preparations as follows:

$$C.U._{specimen+substrate} - C.U._{specimen-substrate} = \Delta C.U._{specimen}$$

$$\Delta C.U._{specimen} = (mx + b)\,\Delta \text{ umol SH/mL/T}$$

T = Reaction time (min)

3) Calculate enzyme activities:

$$U\ ACHe/mL_{RBC} = \Delta \text{ umol SH/mL/min} \times DF_{RBC}$$

$$U\ ACHe/mL_{plasma} = \Delta \text{ umol SH/mL/min} \times DF_{plasma}$$

$$DF_{RBC} = \frac{Vol_{RBC}(mL) + Vol_{diluent}(mL)}{Vol_{RBC}(mL)}$$

$$DF_{plasma} = \frac{Vol_{plasma}(mL) + Vol_{diluent}(mL)}{Vol_{plasma}(mL)}$$

4) Use alternative formula to derive DF_{RBC} from HCT measurements when required

$$\text{Packed cell vol (PCV}^*) = Vol_{WB}(mL) \times HCT/_{100}$$

$$DF_{RBC} = \frac{(PCV + Vol^*_{diluent})}{PCV}$$

* in mL

5) Record results on data sheets in format shown in Figures 2-5.

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

Appendix A

Hardware components - AAII Chemistry Module - ACHe

1) 2 ea (#177E004-02) - 3 input connector

2) 2 ea (#177E004-01) - 2 input connector

3) 2 ea (#157E095-01) - 20 turn coil + terminal injection fitting

4) 2 ea (#A157-0202-01) - 1 turn phasing coil

5) 2 ea (#157-E273-01) - 37° C heating bath, B Coil (5.37 mL)

6) 2 ea (#157-B369-01/ #157B670-01) - 24" dialyzer assembly

7) 2 ea (#170-0103-01) - 5 turn mixing coil

8) 2 ea (#170-0472-02) - Type C dialyzer membranes

9) Misc glass tubing and plastic tubing for custom-fit connections

10) 2 ea AAII manifold trays, shell, covers, and heating bath mounting brackets.

List of Reference Procedure Modifications:

1) 50-fold dilution of Glutathione calibration standards.

2) Saline suspension of intact erythrocytes sampled into AAII system.

3) Separate colorimeters used to monitor absorbance activity in the presence and absence of substrate.

4) Two-channel recorder used for continuous, simultaneous chart record for both channels.

5) Shortened flow pathways prior to point of substrate addition.

6) 24 inch dialyzers

7) Glutathione Stds used to calibrate both channels.

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

(Fig 1)

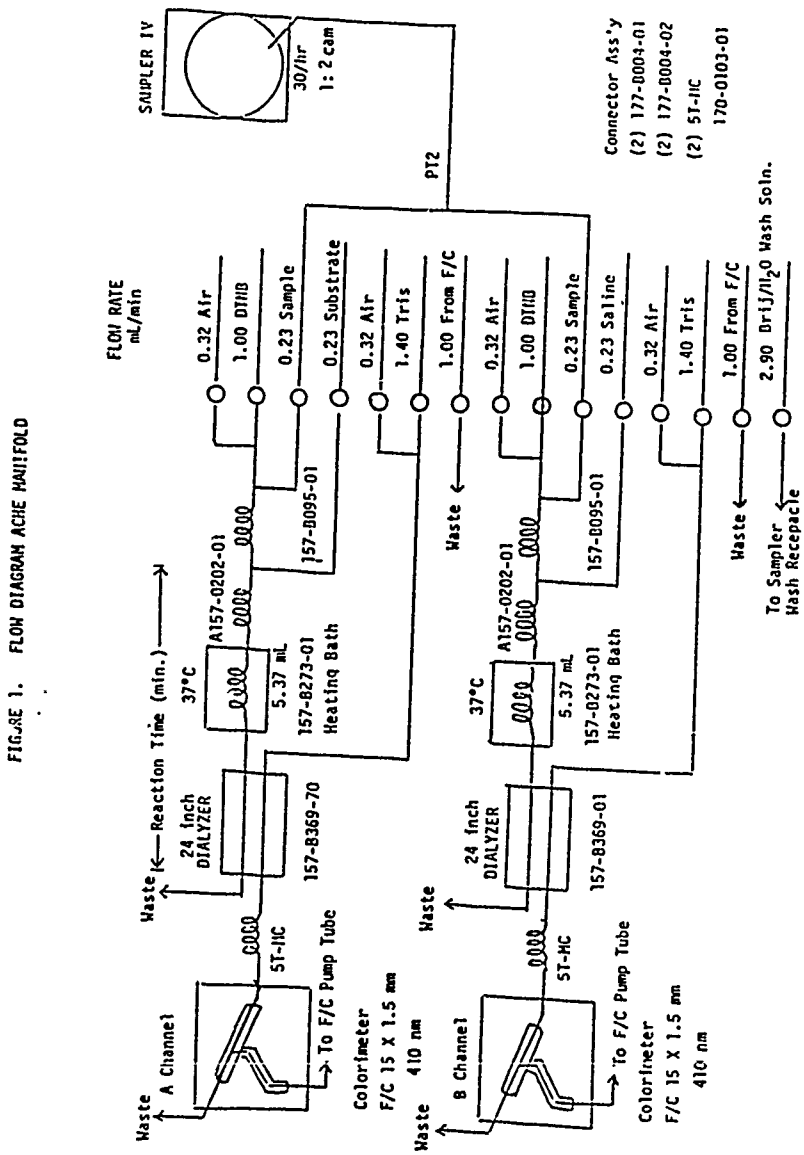

FIGURE 1. FLOW DIAGRAM ACHE MANIFOLD

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

(Fig 2)

PREPARATION OF SAMPLES

Study_____ Assay_____ Date_____ Analyst_____
Code_____ WB Vol._____uL ——→PCV + _____uL_____ DF=_____
Code_____ Vol. RBC_____uL + _____uL_____ DF=_____
Code_____ Vol. Plasma_____uL + _____uL_____ DF=_____
Code_____

Lab #	Specimen I.D. #	HCT R1	HCT R2	HCT Mean	RBC Prep Code	REC DF	COMMENTS
1							
2							
3							
4							
5							
6							
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Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

(Fig 3)

Study_____

Assay_____

Date_____

Analyst_____

STD_____ Stock Prep. Date_____ Stock Conc._____

STD Calibration

Lab I.D.#	X Values (umol/mL)	Y Values (Chart Units, C.U.) + Substrate				- Substrate				

Linear Regression

(y = mx + b), y = _____ X + _____ Numbers of values, n = _____

Correlation Coefficient, r = _____

AA II Reaction Time_____ min. at_____ °C

Control_____ Stock Prep. Date_____ Stock Conc._____

Lab I.D.#	Dilution	△ Chart Units				Activity (U/mL)

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

(Fig 4)

Chart Recorder Data

Study_____

Assay_____

Page____of ____Pages

Date_____

Analyst_____

Lab #	GLP I.D.#	RBC +Subst.	RBC -Subst.	RBC △C.U.	PLASMA +Subst.	PLASMA -Subst.	PLASMA △C.U.	Notes
1								
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Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

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(Fig 5)

RESULTS
Study_________ SOP # _________
Assay_________ Species_________ Date_________

Specimen I.D. #	HCT	RBC UAChe/ml		Plasma UChe/ml	

Appendix G (cont.): PROCEDURES FOR CHOLINESTERASE DETERMINATIONS

SIGNATURES PAGE

Approved: 20 Feb 87
Date

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Certified: 20 Feb 87
Date

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Unit

Appendix H: PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 1 Males

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
530	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
539	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
543*	0.0	0.0	0.0	0.0									
557	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
566	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
577	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
618	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
620*	0.0	0.0	0.0	0.0									
635	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
680*	0.0	0.0	0.0	0.0									
681*	0.0	0.0	0.0	0.0									
688	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
706	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
707	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
712*	0.0	0.0	0.0	0.0									
Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Std Dev	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SEM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

* Interim sacrifice animal.

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 2 Males

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
506*	1.4	1.2	1.0	1.1									
507*	1.1	1.0	0.8	0.8									
531	1.3	1.2	0.9	0.9	0.9	1.1	1.0	0.9	0.9	1.0	1.0	0.9	1.3
548*	1.0	1.0	0.8	0.9									
600	1.1	1.0	0.9	0.9	0.9	1.1	1.0	0.9	0.9	0.9	0.9	0.8	1.3
606*	1.2	1.1	1.0	1.0									
625	1.0	1.0	0.9	0.9	0.8	1.0	1.0	0.9	0.9	0.8	0.9	0.9	1.0
628	1.1	1.0	0.8	0.9	0.8	1.0	1.2	0.9	0.9	0.9	0.9	•	•
634	1.1	1.0	0.8	0.9	0.8	1.0	1.0	•	0.8	0.9	0.8	0.8	1.0
666	1.0	0.9	0.8	0.9	0.9	1.0	1.0	0.8	0.9	0.9	0.8	0.9	1.0
678	1.3	1.0	0.9	0.9	0.8	1.0	1.0	0.8	0.8	0.8	0.8	0.8	1.0
694	1.1	1.0	0.8	0.9	0.7	1.0	0.9	0.8	0.8	1.0	0.8	0.8	0.9
731	1.1	0.9	0.9	0.8	0.8	1.0	0.9	0.8	0.8	0.8	0.9	0.8	1.0
733*	1.0	1.0	0.9	0.9									
734	1.0	1.0	0.9	0.9	0.9	1.0	0.9	0.8	0.8	0.9	0.9	0.8	1.0
Mean	1.1	1.0	0.9	0.9	0.8	1.0	1.0	0.9	0.9	0.9	0.9	0.8	1.1
Std Dev	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1
SEM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 3 Males

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
510*	9.9	9.3	8.4	9.1									
511	8.7	8.6	8.2	8.7	8.3	9.6	10.2	9.9	9.2	9.3	9.2	8.9	9.6
520*	10.2	10.4	9.6	9.9									
526	8.7	8.1	8.0	10.4	8.2	9.4	10.3	9.5	9.2	8.8	9.2	9.6	10.6
544	9.3	8.6	7.7	8.6	7.2	8.3	9.6	9.6	8.7	8.8	9.1	9.6	10.2
553	8.8	8.5	8.3	9.3	8.4	10.8	10.6	10.4	10.0	9.7	9.9	10.0	10.7
581	11.3	9.4	9.7	11.0	9.4	•	11.3	10.8	10.1	9.7	9.6	9.8	10.7
583	8.6	8.6	8.6	9.3	8.3	10.3	10.7	10.7	9.7	9.8	10.4	10.4	10.7
599*	8.5	7.9	8.1	8.6									
602*	10.2	9.7	8.8	9.8									
696	8.2	7.9	7.9	8.5	7.7	9.5	10.0	9.8	8.8	8.6	9.3	8.6	10.0
698	8.5	8.0	•	8.8	7.8	9.8	10.0	9.9	9.6	9.6	9.7	9.3	9.5
713*	10.3	8.9	7.5	9.7									
717	8.7	8.2	8.7	8.6	6.0	8.9	9.6	9.1	8.0	8.9	8.9	•	10.0
723	10.9	9.7	9.4	9.9	8.3	10.0	10.3	10.4	9.8	9.7	9.4	9.0	10.4
Mean	9.4	8.8	8.5	9.4	8.0	9.6	10.3	10.0	9.3	9.3	9.5	9.5	10.2
Std Dev	1.0	0.8	0.7	0.8	0.9	0.7	0.5	0.5	0.7	0.5	0.4	0.6	0.5
SEM	0.3	0.2	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.1

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 4 Males

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
554*	24.8	26.4	25.1	24.6									
593*	26.9	26.8	27.2	26.2									
604*	27.8	26.5	25.0	25.6									
612	29.7	30.2	27.5	27.5	23.6	30.4	25.7	18.2	•	27.7	23.7	27.8	•
626	32.7	33.1	27.9	30.0	26.1	32.0	29.3	19.6	27.3	27.0	25.4	29.6	•
636	35.5	34.7	29.3	29.5	26.7	33.4	29.0	19.1	28.7	29.9	27.3	30.7	31.9
639	26.0	26.7	24.7	24.1	24.8	29.0	27.0	17.5	25.4	26.6	25.3	26.8	30.4
644*	34.4	32.2	29.4	29.6									
645*	26.1	26.5	24.8	24.2									
646	29.8	28.1	27.1	26.5	24.7	30.0	26.4	17.5	27.0	27.2	25.4	28.7	28.6
655	33.2	30.9	29.6	30.2	27.6	35.9	31.0	21.0	30.4	31.0	28.5	32.8	30.9
675	29.1	31.1	29.7	30.6	26.2	29.9	27.9	18.5	26.7	•	25.9	27.7	29.2
676	25.1	28.9	28.6	29.6	25.8	31.5	29.3	20.9	28.6	29.9	26.0	28.6	29.6
703	27.3	28.2	27.2	28.7	25.2	30.3	26.5	17.6	•	•	24.3	28.7	30.2
718	27.2	28.2	25.1	26.7	23.6	30.4	27.3	17.7	25.6	27.3	24.7	26.9	29.6
Mean	29.0	29.2	27.2	27.6	25.4	31.3	27.9	18.8	27.4	28.3	25.7	28.8	30.1
Std Dev	3.4	2.7	1.9	2.3	1.3	2.0	1.7	1.4	1.7	1.7	1.4	1.8	1.0
SEM	0.9	0.7	0.5	0.6	0.4	0.6	0.5	0.4	0.6	0.6	0.4	0.6	0.4

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 5 Males

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
509*	50.4	65.6	54.9	57.2									
533*	49.3	70.7	58.2	61.0									
550	53.2	70.7	61.2	62.1	61.1	66.1	66.7	68.7	64.9	•	68.7	64.3	70.9
570	52.3	58.2	52.8	53.9	55.1	57.3	60.1	59.2	60.1	55.8	60.6	57.0	64.3
617	52.5	58.2	50.7	50.0	54.3	57.1	58.9	59.5	58.9	57.6	60.5	58.9	63.6
621*	61.2	67.8	59.2	57.8									
632	50.7	55.7	47.6	50.9	50.8	53.6	56.1	60.1	55.1	51.5	55.1	54.8	62.9
641	55.7	67.2	58.3	57.2	58.8	59.2	63.1	65.2	60.9	56.5	61.0	57.1	66.3
648*	59.0	52.1	49.6	52.1									
684	46.9	70.5	56.8	56.4	55.8	59.8	63.0	62.2	58.9	58.1	61.1	56.6	64.7
686	48.9	•	51.4	54.8	49.4	58.2	59.7	58.6	57.6	55.2	63.9	59.0	64.1
689	54.0	60.2	50.2	53.6	56.3	55.9	58.4	58.0	53.8	48.9	58.3	51.7	57.6
690	75.5	78.9	61.3	66.5	80.1	64.3	65.9	68.6	65.0	55.7	66.3	61.0	64.9
699	55.0	58.6	49.4	50.9	44.3	50.7	58.5	57.4	55.2	52.7	57.6	56.2	56.0
726*	56.8	61.5	52.4	55.8									
Mean	54.8	64.0	54.3	56.0	56.6	58.2	61.0	61.8	59.0	54.7	61.3	57.7	63.5
Std Dev	6.9	7.4	4.6	4.6	9.6	4.6	3.5	4.3	3.9	3.0	4.1	3.4	4.2
SEM	1.8	2.0	1.2	1.2	3.0	1.4	1.1	1.4	1.2	1.0	1.3	1.1	1.3

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 6 Males

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
523*	65.5	106.9	88.5	90.3									
552*	46.1	115.6	83.5	89.0									
563	•	121.4	90.3	95.6	82.5	104.3	97.9	110.0	89.3	92.1	89.2	96.1	132.3
565	62.4	104.0	82.7	83.1	72.4	93.4	88.2	97.5	84.4	87.3	84.9	87.0	127.8
568	73.5	122.8	93.7	98.9	86.6	108.7	99.0	113.5	91.9	101.9	95.0	98.3	139.8
587*	58.2	109.6	75.0	80.4									
607	78.7	107.3	77.8	74.7	74.1	91.0	81.2	97.6	79.5	88.1	84.0	90.0	121.1
630	70.9	113.1	84.8	85.2	73.4	95.0	88.7	98.5	82.9	90.5	87.9	•	129.3
631*	61.0	105.3	86.3	87.6									
652	80.9	107.3	85.2	83.9	75.5	98.7	88.1	100.8	80.4	88.3	84.1	87.2	134.4
659	75.5	108.8	89.5	85.1	74.6	94.9	89.8	101.1	82.4	86.7	83.2	83.4	131.0
674*	62.5	90.6	93.7	89.3									
679	75.7	102.5	73.2	72.4	67.2	83.3	77.4	92.5	73.3	78.8	75.9	81.6	121.0
708	61.7	102.3	80.4	81.5	71.8	94.0	86.5	92.8	71.5	•	80.4	85.3	125.5
728	66.2	98.3	80.9	82.5	94.2	92.8	75.8	94.5	93.6	91.5	85.4	77.4	130.7
Mean	67.0	107.7	84.4	85.3	77.2	95.6	87.3	99.9	81.9	89.5	85.0	87.3	129.3
Std Dev	9.4	8.3	6.2	7.0	8.1	7.0	7.6	7.0	6.3	6.1	5.1	6.7	5.8
SEM	2.4	2.1	1.6	1.8	2.6	2.2	2.4	2.2	2.0	2.0	1.6	2.2	1.8

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 1 Females

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
765*	0.0	0.0	0.0	0.0									
768	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
772	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
776	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
778	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
806	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
810	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
814*	0.0	0.0	0.0	0.0									
815*	0.0	0.0	0.0	0.0									
818	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
825*	0.0	0.0	0.0	0.0									
832*	0.0	0.0	0.0	0.0									
833	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
843	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
849	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Std Dev	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SEM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

* Interim sacrifice animal.

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 2 Females

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
752	0.9	0.8	0.9	0.8	1.0	0.8	0.9	0.8	0.9	0.9	0.9	1.3	0.8
755	1.0	0.9	0.9	1.0	1.1	0.8	0.9	0.9	1.0	0.9	0.9	1.0	0.8
758*	1.1	1.0	1.0	0.9									
764	1.0	0.8	0.8	0.9	1.0	0.7	1.1	0.7	0.8	0.8	0.9	1.2	0.9
774	1.1	1.0	1.0	0.8	1.1	0.9	0.9	0.8	0.9	0.9	0.8	1.1	0.9
781*	1.0	0.9	0.9	0.8									
795	1.1	1.0	1.0	0.6	1.3	1.0	1.1	0.8	1.0	0.9	0.8	1.2	0.9
799*	1.0	0.9	0.9	0.8									
804	0.9	0.9	0.9	0.8	1.1	0.8	0.8	0.9	0.8	0.9	0.7	1.3	0.9
829*	1.0	0.8	0.9	0.8									
837*	1.0	0.9	1.0	0.7									
838	0.9	0.8	0.9	0.9	1.1	0.7	0.9	0.9	1.0	0.9	0.8	1.4	0.9
840	0.9	0.8	0.8	0.8	1.0	0.8	0.8	0.8	0.9	0.9	0.8	1.2	0.8
850	1.0	0.9	0.9	0.9	1.1	0.8	0.9	1.0	0.9	0.8	0.9	1.4	1.1
855	0.9	0.8	0.8	0.8	0.9	0.7	0.8	0.8	0.9	•	0.8	1.2	0.9
Mean	1.0	0.9	0.9	0.8	1.1	0.8	0.9	0.9	0.9	0.9	0.8	1.2	0.9
Std Dev	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1
SEM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 3 Females

Animal# £6D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
749	10.4	10.0	9.7	11.1	10.2	12.0	11.2	10.9	9.4	10.8	9.7	13.9	10.6
751	10.5	9.1	9.2	9.3	10.0	8.9	9.1	10.0	9.9	10.4	8.6	12.4	8.2
753	11.2	8.6	8.3	8.9	9.7	9.2	9.1	10.3	9.6	9.6	6.7	11.4	10.0
759*	10.4	8.7	7.7	8.3									
761	10.9	9.6	9.4	9.5	10.1	9.2	10.0	10.3	9.2	9.1	11.1	14.6	8.9
771*	9.4	7.9	8.6	9.3									
784	9.9	8.5	8.2	9.0	8.5	8.6	8.8	9.5	8.0	9.4	7.6	9.8	9.7
789*	9.9	9.3	9.0	9.6									
802	9.1	9.4	9.1	8.8	10.3	9.1	10.5	8.9	8.4	8.8	8.2	12.2	10.2
803	10.6	10.5	9.9	9.9	11.2	10.7	10.5	9.8	9.2	8.9	7.9	11.9	10.2
805	10.8	10.5	10.1	9.4	9.9	9.4	10.2	10.9	8.9	11.2	9.9	12.1	10.4
826	10.9	10.0	10.1	8.9	8.8	9.3	9.0	9.0	6.4	8.6	•	10.1	8.9
827	10.4	9.3	8.2	8.1	9.5	8.8	10.2	9.0	9.0	9.0	8.6	12.5	10.6
846*	11.3	9.6	8.8	9.8									
852*	10.7	•	9.2	9.5									
Mean	10.4	9.4	9.0	9.3	9.8	9.5	9.9	9.8	8.8	9.6	8.7	12.1	9.7
Std Dev	0.6	0.7	0.7	0.7	0.8	1.0	0.8	0.8	1.0	0.9	1.4	1.5	0.8
SEM	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.5	0.5	0.3

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 4 Females

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
766	36.7	32.9	30.3	34.8	31.0	32.8	32.3	34.8	32.8	32.7	34.9	37.6	34.7
780	30.7	28.8	27.5	28.1	26.7	26.4	28.5	28.1	27.9	27.9	27.1	35.4	33.6
785*	32.4	31.0	29.3	29.5									
787	28.5	38.6	26.1	25.1	26.5	24.4	25.4	26.5	24.7	28.3	23.9	33.7	28.2
790*	32.2	30.7	30.4	29.2									
793	30.9	28.0	28.5	28.3	27.0	27.6	39.8	28.5	25.8	28.7	27.3	33.8	29.5
794*	28.7	27.9	27.1	25.4									
811	33.9	29.2	28.0	29.3	29.7	30.6	31.0	31.6	33.1	32.6	30.2	37.9	34.0
812	33.3	28.2	26.6	26.3	27.9	27.1	28.1	27.8	30.4	28.3	23.2	34.7	30.3
821*	34.2	29.4	27.4	30.7									
842*	28.2	25.2	25.2	26.1									
844	31.2	30.3	27.6	27.6	26.4	28.7	27.4	28.9	29.2	29.6	28.0	34.1	30.6
848	29.3	29.8	25.6	26.5	26.8	26.5	27.0	27.0	26.8	28.1	24.9	29.8	25.4
851	34.3	29.1	26.5	31.2	28.0	30.2	31.8	34.4	30.5	32.3	28.7	42.0	37.5
854	35.2	30.0	30.0	31.8	30.7	29.7	29.3	28.1	29.2	30.4	25.2	36.6	29.2
Mean	32.0	29.9	27.7	28.7	28.1	28.4	30.1	29.6	29.0	29.9	27.4	35.6	31.3
Std Dev	2.6	3.0	1.7	2.7	1.8	2.5	4.1	3.0	2.8	2.0	3.5	3.2	3.6
SEM	0.7	0.8	0.4	0.7	0.6	0.8	1.3	0.9	0.9	0.6	1.1	1.0	1.1

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 5 Females

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
760	•	•	•	•	•	•	•	•	•	•	•	•	•
762	61.4	72.4	60.6	58.6	64.6	61.3	61.1	58.4	61.6	63.9	55.4	80.8	66.6
769	57.2	60.7	52.8	61.7	63.5	60.0	•	55.5	63.8	62.0	50.9	67.2	61.3
770	56.4	64.9	62.6	56.7	59.4	55.8	63.6	61.9	62.4	56.4	51.5	58.8	54.6
775*	54.6	57.4	47.7	51.2									
782*	55.9	63.8	55.5	55.3									
797*	56.7	68.1	68.1	57.6									
819	54.9	61.3	53.3	51.2	58.0	52.8	52.7	52.2	60.6	58.0	53.5	69.6	59.4
820	51.7	58.0	55.8	•	58.4	52.8	60.6	69.3	57.3	56.1	48.9	67.5	67.9
831	42.7	67.3	57.5	56.0	61.0	60.7	60.2	60.7	58.0	60.8	60.9	72.6	64.1
835*	56.2	60.7	56.8	55.1									
841*	52.9	62.1	62.2	59.5									
845	60.8	65.3	58.9	56.2	63.6	65.1	57.7	59.8	64.2	64.6	61.5	70.3	57.8
847	45.1	63.4	54.7	53.7	58.1	56.1	59.5	55.5	62.8	61.6	54.0	67.9	66.5
856	59.7	65.3	57.1	52.5	59.7	59.9	52.1	62.6	59.3	58.5	58.0	72.8	64.6
Mean	54.7	63.6	57.4	55.8	60.7	58.3	58.5	59.6	61.1	60.2	55.0	69.7	62.5
Std Dev	5.4	4.0	5.0	3.1	2.6	4.1	4.1	5.0	2.5	3.1	4.4	5.9	4.5
SEM	1.4	1.0	1.3	0.8	0.8	1.3	1.4	1.6	0.8	1.0	1.4	1.9	1.4

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix H (cont.): PYRIDOSTIGMINE CONSUMPTION (mg/kg/day)

Group 6 Females

Animal# 86D00-	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
750	62.2	115.9	93.7	81.2	83.2	80.9	87.9	76.7	88.2	•	87.4	97.2	88.7
754*	65.9	114.4	92.5	81.1									
757*	78.2	112.7	99.9	87.7									
773*	79.3	118.6	90.3	80.0									
779*	63.2	115.9	95.0	93.5									
783	89.1	133.6	102.2	85.3	95.1	81.1	92.0	73.2	86.3	99.8	114.4	113.5	103.7
792	61.9	122.7	96.7	77.9	78.1	80.7	86.5	72.8	90.8	92.3	100.0	103.5	89.9
798	67.5	103.0	98.3	85.5	86.8	95.6	•	100.6	96.1	102.3	109.2	112.0	95.0
809	70.6	128.5	96.3	92.9	87.1	82.7	88.2	86.1	88.5	85.6	91.6	97.2	87.8
813	79.2	122.3	108.3	87.4	87.3	86.8	97.3	93.6	98.2	98.0	120.5	110.1	105.3
816	81.4	121.2	107.8	100.2	99.4	102.0	103.5	101.9	98.1	101.5	102.6	111.1	101.5
817	•	100.0	88.7	80.8	78.7	85.8	84.2	83.9	87.1	85.9	100.2	117.5	93.1
822	79.6	115.3	86.2	78.1	87.2	83.5	84.1	79.8	91.4	90.0	89.8	105.7	86.4
830	79.2	103.4	86.3	77.1	74.8	82.3	79.3	77.8	82.0	88.8	85.8	98.3	84.8
839*	76.9	125.8	102.2	81.3									
Mean	73.9	116.9	96.3	84.7	85.8	86.1	89.2	84.6	90.7	93.8	100.2	106.6	93.6
Std Dev	8.5	9.5	7.0	6.7	7.6	7.1	7.4	10.8	5.4	6.7	11.8	7.3	7.5
SEM	2.3	2.5	1.8	1.7	2.4	2.3	2.5	3.4	1.7	2.2	3.7	2.3	2.4

* Interim sacrifice animal.
• Unable to calculate due to incomplete food consumption data (spill).

Appendix I: FOOD CONSUMPTION (g/week)

Group 1 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
530	152	172	164	147	171	159	166	160	159	159	170	166	162	spill
539	132	153	165	165	161	146	150	157	165	151	182	164	167	163
543*	149	174	180	178	208									
557	171	188	185	187	188	192	192	192	188	181	178	177	189	186
566	170	186	188	184	202	188	186	194	190	185	199	spill	204	224
577	185	222	215	204	206	203	202	195	198	195	204	191	203	206
618	108	174	175	172	173	177	193	185	177	182	175	177	175	170
620*	178	165	168	184	180									
635	142	181	168	164	170	168	161	172	174	177	179	164	181	178
680*	134	196	170	174	157									
681*	130	147	163	150	171									
688	136	148	152	150	154	166	159	156	159	198	158	160	165	162
706	134	150	153	152	155	151	143	138	144	181	147	121	147	150
707	149	165	166	159	161	171	164	161	176	179	190	180	179	168
712*	152	157	156	153	151									
Mean	148.1	171.9	171.2	168.2	173.9	172.1	171.6	171.0	173.0	178.8	178.2	166.7	177.2	178.6
Std Dev	20.8	20.7	16.1	16.9	19.2	18.2	20.1	19.6	16.5	14.4	17.4	19.8	18.1	23.4
SEM	5.4	5.3	4.2	4.4	5.0	5.8	6.4	6.2	5.2	4.5	5.5	6.6	5.7	7.8

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 2 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
506*	spill	198	198	192	206									
507*	154	176	177	171	174									
531	112	148	164	148	158	159	162	171	173	174	190	178	164	203
548*	120	148	163	155	157									
600	161	166	170	181	187	179	185	199	210	199	205	192	186	235
606*	111	142	175	183	188									
625	146	159	166	176	163	159	161	184	184	173	170	170	190	178
628	147	159	170	166	173	163	160	211	182	172	183	173	spill	spill
634	140	158	166	164	164	162	160	187	spill	167	169	150	158	160
666	159	163	152	162	179	168	157	173	167	172	177	157	162	164
678	139	191	168	172	177	166	166	188	170	163	153	156	164	171
694	155	167	169	160	170	137	162	175	171	166	196	158	155	155
731	160	174	170	178	169	165	174	170	174	172	170	165	158	159
733*	152	157	172	170	166									
734	136	154	155	164	160	161	168	165	166	162	165	160	157	160
Mean	142.3	164.0	169.0	169.5	172.7	161.9	165.5	182.3	177.4	172.0	177.8	165.9	166.0	176.1
Std Dev	17.1	15.5	10.4	11.5	13.3	10.5	8.4	14.4	13.7	10.4	15.7	12.6	12.9	26.5
SEM	4.6	4.0	2.7	3.0	3.4	3.3	2.7	4.6	4.6	3.3	5.0	4.0	4.3	8.8

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 3 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
510*	156	178	187	182	198									
511	155	158	167	164	168	173	166	170	179	173	177	166	158	160
520*	212	178	204	204	215									
526	128	142	138	138	173	145	137	145	145	145	139	136	139	146
544	143	162	162	152	165	147	141	159	173	163	166	166	174	175
553	158	178	181	181	197	188	201	193	205	205	204	199	200	203
581	129	151	141	159	191	182	spill	187	198	195	191	182	182	190
583	171	180	186	192	200	193	202	206	224	212	217	223	226	222
599*	132	147	145	155	160									
602*	133	162	168	159	175									
696	149	152	148	151	157	152	154	157	167	156	155	161	147	161
698	152	159	154	spill	167	158	165	162	173	176	179	173	163	158
713*	133	197	189	163	207									
717	166	183	180	188	182	138	169	178	182	164	182	174	spill	181
723	117	145	151	159	168	155	156	158	175	175	177	164	155	169
Mean	148.9	164.8	166.7	167.6	181.5	163.1	165.7	171.5	182.1	176.4	178.7	174.4	171.6	176.5
Std Dev	23.3	16.5	20.3	18.7	18.4	19.4	23.0	19.1	22.0	21.6	22.5	23.4	27.6	23.1
SEM	6.0	4.3	5.3	5.0	4.8	6.1	7.7	6.0	7.0	6.8	7.1	7.4	9.2	7.3

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 4 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
554*	140	151	166	168	165									
593*	170	178	180	192	185									
604*	158	178	173	173	178									
612	153	200	220	218	221	200	213	206	231	spill	226	208	210	spill
626	129	151	172	160	178	167	172	185	201	177	172	175	176	spill
636	127	150	163	151	155	152	160	161	171	164	169	167	160	167
639	158	169	176	168	160	173	168	179	183	167	172	174	156	177
644*	131	159	170	172	180									
645*	152	157	163	161	158									
646	146	171	171	178	177	175	175	176	185	181	179	180	174	173
655	140	154	155	158	165	162	174	175	191	176	178	176	173	166
675	146	134	154	163	174	160	152	164	173	158	spill	164	148	154
676	153	150	181	194	204	187	187	201	228	197	204	190	177	181
703	148	158	168	173	183	169	168	169	178	spill	spill	163	164	171
718	133	150	160	152	163	153	163	167	171	157	167	161	149	163
Mean	145.6	160.7	171.5	172.1	176.4	169.8	173.2	178.3	191.2	172.1	183.4	175.8	168.7	169.0
Std Dev	12.3	16.1	15.7	17.8	17.7	14.9	16.9	15.1	22.3	13.4	20.8	14.4	18.1	8.5
SEM	3.2	4.2	4.0	4.6	4.6	4.7	5.3	4.8	7.0	4.7	7.3	4.5	5.7	3.0

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 5 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
509*	112	108	147	150	161									
533*	110	103	156	160	174									
550	128	111	153	161	169	162	168	158	169	171	spill	170	164	168
570	155	166	181	191	196	193	194	191	194	208	205	196	189	196
617	162	162	175	175	169	174	176	169	175	181	187	172	171	170
621*	105	126	154	166	168									
632	131	136	147	144	152	144	145	141	156	151	149	139	140	147
641	155	143	181	190	189	191	189	191	206	203	200	189	180	193
648*	121	165	151	168	176									
684	106	90	143	144	148	144	151	152	157	158	167	155	147	156
686	143	136	spill	158	168	147	167	160	162	166	164	166	158	157
689	156	169	187	183	197	200	191	184	187	182	173	179	161	165
690	111	158	182	173	193	228	178	172	188	191	175	183	173	172
699	138	167	178	174	178	151	164	172	174	177	180	172	171	156
726*	182	173	187	186	195									
Mean	134.3	140.9	165.9	168.2	175.5	173.4	172.3	169.0	176.8	178.8	177.8	172.1	165.4	168.0
Std Dev	23.9	27.7	16.9	15.5	15.8	28.8	16.5	16.6	16.6	18.4	17.6	16.5	14.7	15.9
SEM	6.2	7.1	4.5	4.0	4.1	9.1	5.2	5.3	5.3	5.8	5.9	5.2	4.7	5.0

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 6 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
523*	127	79	116	143	161									
552*	155	67	141	145	164									
563	140	129	156	170	197	194	194	199	216	200	198	198	198	191
565	136	97	139	157	168	163	164	167	176	172	169	169	160	164
568	154	117	175	194	219	216	213	210	231	211	223	217	210	211
587*	144	95	157	149	165									
607	163	151	182	183	181	198	189	180	206	189	200	198	196	184
630	144	115	162	173	184	174	175	177	188	180	188	189	spill	181
631*	145	96	141	165	180									
652	133	119	137	154	160	160	165	159	171	153	160	156	149	160
659	131	91	122	149	154	151	150	154	166	153	154	153	142	156
674*	145	90	115	172	180									
679	170	140	172	171	174	172	164	167	189	168	172	170	169	176
708	171	112	159	176	187	181	184	184	186	158	spill	173	170	176
728	171	104	134	155	166	208	159	139	163	164	173	166	138	163
Mean	148.6	106.8	147.2	163.7	176.0	181.7	175.7	173.6	189.2	174.8	181.9	178.9	170.2	176.2
Std Dev	14.8	22.6	21.0	14.9	16.8	21.6	19.1	21.1	22.3	19.9	22.1	20.7	26.0	16.7
SEM	3.8	5.8	5.4	3.9	4.3	6.8	6.1	6.7	7.1	6.3	7.4	6.5	8.7	5.3

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 1 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
765*	116	112	110	109	120									
768	104	103	spill	110	114	117	119	107	116	91	112	105	111	112
772	106	99	89	spill	108	98	104	117	107	spill	97	98	93	108
776	108	110	110	114	97	113	104	97	107	86	110	87	96	100
778	111	123	115	123	124	120	121	115	119	107	111	104	118	116
806	125	128	111	116	114	118	113	109	109	99	108	112	112	124
810	119	130	116	140	117	126	123	131	120	120	122	111	120	131
814*	111	112	122	118	108									
815*	109	117	117	119	105									
818	113	118	119	123	144	123	103	120	129	117	113	118	115	108
825*	102	119	113	114	114									
832*	spill	127	129	137	132									
833	111	109	120	115	119	113	103	114	101	102	88	94	115	117
843	125	129	131	136	138	143	129	126	136	122	122	119	125	127
849	106	142	125	132	130	135	120	124	121	122	111	110	127	132
Mean	111.9	118.5	116.2	121.9	118.9	120.6	113.9	116.0	116.5	107.3	109.4	105.8	113.2	117.5
Std Dev	7.2	11.5	10.3	10.4	12.8	12.4	9.8	10.0	10.8	13.7	10.3	10.3	11.1	10.8
SEM	1.9	3.0	2.7	2.8	3.3	3.9	3.1	3.2	3.4	4.6	3.3	3.3	3.5	3.4

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 2 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
752	109	114	109	117	109	118	110	111	110	109	106	106	112	103
755	119	127	126	121	140	138	128	125	131	137	123	103	85	102
758*	153	158	164	173	167									
764	112	124	121	117	128	127	117	160	110	110	110	112	118	126
774	128	147	153	152	137	147	161	145	136	137	144	124	115	136
781*	122	136	129	136	124									
795	134	140	157	151	95	177	186	180	131	175	166	135	145	157
799*	112	128	125	130	117									
804	139	128	139	138	119	137	131	125	143	125	141	96	125	135
829*	98	105	98	105	97									
837*	116	115	116	128	101									
838	106	101	95	104	104	108	95	102	108	110	103	89	110	107
840	126	126	130	135	129	145	145	137	137	139	139	113	135	139
850	107	117	116	116	120	119	107	114	127	113	100	98	115	139
855	107	119	108	109	111	108	109	114	113	118	spill	95	115	125
Mean	119.2	125.7	125.7	128.8	119.9	132.4	128.9	131.3	124.6	127.3	125.8	107.1	117.5	126.9
Std Dev	14.7	15.2	20.5	19.3	19.0	21.1	28.0	24.4	13.1	20.6	22.9	14.2	15.9	18.1
SEM	3.8	3.9	5.3	5.0	4.9	6.7	8.9	7.7	4.1	6.5	7.6	4.5	5.0	5.7

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 3 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
749	111	125	127	123	134	122	135	129	127	114	118	99	122	112
751	128	143	140	144	138	146	123	129	142	147	146	113	138	107
753	114	133	116	115	116	123	113	117	133	130	123	78	112	119
759*	112	131	120	106	109									
761	spill	128	129	131	128	135	115	128	136	127	115	138	166	119
771*	130	124	109	119	126									
784	116	145	140	136	141	133	126	133	146	130	139	106	118	140
789*	128	135	141	139	144									
802	124	121	139	143	132	153	128	154	132	128	123	106	136	138
803	156	167	173	172	164	185	172	179	171	168	151	125	161	169
805	135	133	141	142	126	128	111	124	137	115	133	112	117	121
826	156	150	155	168	144	136	134	132	129	97	120	spill	110	117
827	127	132	134	121	112	127	108	122	110	117	106	94	117	121
846*	143	151	146	139	147									
852*	131	122	spill	120	121									
Mean	129.4	136.0	136.4	134.5	132.1	138.8	126.5	134.7	136.3	127.3	127.4	107.9	129.7	126.3
Std Dev	14.5	12.9	16.3	18.4	14.8	18.9	18.6	18.4	15.6	19.5	14.4	17.4	20.1	18.2
SEM	3.9	3.3	4.3	4.8	3.8	6.0	5.9	5.8	4.9	6.2	4.5	5.8	6.3	5.7

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 4 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
766	124	136	133	125	135	132	133	130	137	130	123	131	123	134
780	139	119	123	122	117	120	113	122	119	117	111	105	122	144
785*	164	149	159	159	152									
787	127	113	169	121	108	122	109	113	116	105	115	96	116	117
790*	140	148	156	165	153									
793	144	138	133	141	133	137	135	197	137	121	126	118	128	134
794*	140	132	138	140	120									
811	spill	138	132	131	126	136	134	136	134	137	129	116	125	133
812	123	151	141	140	127	143	135	142	137	148	132	105	135	140
821*	115	138	129	124	131									
842*	116	121	111	114	113									
844	133	134	138	133	126	127	130	124	128	129	125	115	118	124
848	116	117	129	118	115	124	117	121	119	119	119	102	105	106
851	116	131	120	113	126	121	124	131	140	124	124	106	133	143
854	spill	139	129	133	130	137	128	126	118	121	120	97	121	113
Mean	130.5	133.6	136.0	131.9	127.5	129.9	125.8	134.2	128.5	125.1	122.4	109.1	122.6	128.8
Std Dev	14.6	11.7	15.3	15.2	12.7	8.1	9.6	23.5	9.6	11.8	6.3	10.8	8.7	13.2
SEM	4.0	3.0	4.0	3.9	3.3	2.6	3.1	7.4	3.0	3.7	2.0	3.4	2.7	4.2

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 5 Females

Animal# 86D00-	QWK2[@]	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
760	NR[†]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
762	127	130	142	135	127	132	124	125	110	112	113	96	128	122
769	119	133	132	125	142	144	137	spill	118	131	125	101	119	124
770	122	131	142	154	139	142	132	152	141	140	122	107	108	114
775*	106	120	122	112	115									
782*	126	132	143	137	131									
797*	145	139	156	185	156									
819	126	133	144	141	128	138	125	125	113	128	121	109	128	125
820	127	120	121	122	spill	123	109	122	132	110	103	86	106	123
831	117	94	135	129	122	128	127	127	119	111	112	111	121	122
835*	119	123	121	124	117									
841*	111	107	115	125	116									
845	130	141	143	142	132	143	149	136	130	136	133	129	135	125
847	132	112	144	139	132	138	132	141	122	134	129	111	126	142
856	113	122	126	123	110	119	119	104	117	109	103	101	118	119
Mean	122.9	124.1	134.7	135.2	128.2	134.1	128.2	129.0	122.4	123.4	117.9	105.7	121.0	124.0
Std Dev	9.9	13.0	12.0	17.9	12.7	9.1	11.3	14.3	10.0	12.7	10.8	11.9	9.5	7.6
SEM	2.6	3.5	3.2	4.8	3.5	3.0	3.8	5.1	3.3	4.2	3.6	4.0	3.2	2.5

[@] Quarantine week 2.
[†] Not recorded.
* Interim sacrifice animal.

Appendix I (cont.): FOOD CONSUMPTION (g/week)

Group 6 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
750	128	87	127	135	134	136	131	141	121	127	spill	105	122	125
754*	103	83	115	122	123									
757*	120	100	113	129	132									
773*	118	106	128	128	130									
779*	128	87	125	132	152									
783	136	132	160	157	144	160	138	154	118	124	141	137	148	152
792	95	74	112	115	106	105	107	113	92	104	106	96	103	100
798	131	94	108	131	131	132	147	spill	152	137	145	129	140	132
809	123	91	135	136	155	149	141	149	144	137	133	119	135	137
813	124	108	132	152	139	135	129	143	138	133	130	135	133	142
816	136	100	117	134	143	143	146	147	144	127	128	107	124	127
817	119	spill	102	120	125	119	130	129	128	123	118	115	144	128
822	118	100	114	110	110	121	117	117	107	110	108	89	110	100
830	119	108	114	125	126	120	130	125	121	114	121	98	121	117
839*	108	88	111	116	102									
Mean	120.4	97.0	120.9	129.5	130.1	132.0	131.6	135.3	126.5	123.6	125.6	113.0	128.0	126.0
Std Dev	11.5	14.2	14.3	12.8	15.6	16.3	12.5	14.8	18.6	11.2	13.5	16.8	14.6	16.8
SEM	3.0	3.8	3.7	3.3	4.0	5.1	4.0	4.9	5.9	3.5	4.5	5.3	4.6	5.3

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J: WATER CONSUMPTION (ml/week)

Group 1 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
530	196	224	214	218	229	218	218	213	215	200	214	213	217	201
539	237	316	318	316	287	282	275	289	284	250	309	310	299	275
543*	305	375	378	411	437									
557	237	251	257	267	276	244	232	229	224	206	202	207	205	393
566	244	243	289	285	294	292	284	269	269	239	287	282	294	338
577	234	261	271	272	264	236	257	250	232	236	256	249	250	260
618	225	255	269	271	271	271	274	269	249	249	240	243	245	233
620*	222	255	242	258	277									
635	214	279	253	280	281	266	257	256	266	261	244	239	238	235
680*	203	249	242	247	323									
681*	159	250	284	277	306									
688	230	236	238	spill	266	280	261	268	306	250	288	271	285	277
706	186	215	214	216	294	212	201	209	215	214	245	250	256	221
707	245	291	297	302	315	332	309	337	386	382	350	345	384	324
712*	190	201	200	203	205									
Mean	221.8	260.1	264.4	273.1	288.3	263.3	256.8	258.9	264.6	248.7	263.5	260.9	267.3	275.7
Std Dev	33.8	42.8	45.5	51.2	51.1	36 6	32.2	37.8	52.4	51.2	45.1	42.5	51.5	59.9
SEM	8.7	11.1	11.8	13.7	13.2	11.6	10.2	12.0	16.6	16.2	14.2	13.5	16.3	18.9

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 2 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
506*	144	359	346	346	398									
507*	209	224	215	220	219									
531	214	300	310	288	302	301	286	293	288	282	322	297	294	464
548*	173	192	206	196	193									
600	197	232	248	310	284	265	253	288	280	257	275	264	266	285
606*	189	236	275	281	266									
625	191	200	215	234	234	218	215	262	236	214	225	243	229	194
628	207	239	239	239	241	225	211	251	229	226	237	265	278	246
634	221	251	265	265	272	273	264	306	288	284	301	279	304	spill
666	296	393	320	353	398	374	362	351	380	390	337	334	328	328
678	182	249	219	222	215	195	191	202	191	186	160	175	174	185
694	177	198	200	189	213	166	165	186	175	167	195	161	160	152
731	195	229	239	249	248	223	239	246	237	223	229	226	231	219
733*	261	288	308	344	368									
734	195	232	248	257	263	238	232	240	258	263	251	290	287	252
Mean	203.4	254.8	256.9	266.2	274.3	247.8	241.8	262.5	256.2	249.2	253.2	253.4	255.1	258.3
Std Dev	36.4	57.7	45.8	53.3	65.9	59.0	55.0	49.1	58.0	62.9	56.0	53.9	55.5	93.8
SEM	9.4	14.9	11.8	13.7	17.0	18.6	17.4	15.5	18.3	19.9	17.7	17.1	17.6	31.3

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 3 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
510*	234	293	307	298										
511	252	288	310	293	285	259	303	267	256	254	spill	274	244	243
520*	283	325	333	329	308									
526	181	204	209	209	227	207	237	218	233	208	210	227	214	208
544	224	240	222	199	224	181	199	194	201	183	188	210	198	188
553	227	289	302	281	294	315	304	287	306	310	297	313	314	296
581	400	382	453	spill	429	spill	406	399	399	342	375	484	311	297
583	202	226	246	255	262	253	273	266	287	248	472	272	296	261
599*	185	210	212	236	225									
602*	196	259	273	242	260									
696	228	spill	212	224	216	192	194	194	211	138	195	206	206	193
698	211	265	312	338	284	276	284	270	280	277	347	272	263	253
713*	219	321	323	338	328									
717	266	316	282	297	307	274	283	283	296	272	315	314	302	307
723	223	275	253	235	250	222	249	239	257	234	260	251	232	237
Mean	235.4	278.1	283.3	269.6	278.5	242.1	273.2	261.7	272.6	246.6	295.4	282.3	258.0	248.3
Std Dev	53.5	49.3	63.9	47.4	56.1	44.4	60.9	59.3	56.7	59.8	94.0	80.3	45.3	43.1
SEM	13.8	13.2	16.5	12.7	15.0	14.8	19.3	18.8	17.9	18.9	31.3	25.4	14.3	13.6

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 4 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
554*	211	215	222	221	225									
593*	213	241	232	246	249									
604*	220	246	237	239	253									
612	211	273	288	310	307	273	282	278	289	288	288	264	308	289
626	203	235	238	279	288	277	265	283	289	257	287	282	279	180
636	357	409	409	402	364	376	343	335	326	311	302	317	336	275
639	195	256	223	232	213	207	227	217	215	199	219	207	203	197
644*	178	211	232	225	235									
645*	201	260	265	249	271									
646	171	216	222	219	221	190	204	199	201	196	192	187	196	178
655	216	273	270	262	278	255	267	272	283	286	272	297	285	253
675	217	227	236	235	228	205	189	197	194	195	184	187	168	173
676	246	318	338	335	360	328	354	328	329	316	333	297	274	281
703	247	287	298	301	302	313	328	323	306	278	341	327	323	331
718	200	254	268	271	293	271	281	263	264	252	250	242	240	234
Mean	219.1	261.4	265.2	268.4	272.5	269.5	274.0	269.5	269.6	257.8	266.8	260.7	261.2	239.1
Std Dev	43.3	50.2	51.9	50.7	47.5	59.0	56.4	51.5	49.9	46.7	54.8	52.5	57.2	55.3
SEM	11.2	13.0	13.4	13.1	12.3	18.7	17.8	16.3	15.8	14.8	17.3	16.6	18.1	17.5

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 5 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
509*	190	228	268	273	160									
533*	173	140	233	258	272									
550	253	308	300	335	315	300	298	270	248	254	262	244	244	229
570	230	252	265	283	287	281	276	262	267	265	265	277	251	254
617	193	221	185	264	263	268	276	262	270	269	270	282	338	262
621*	239	237	210	221	233									
632	160	192	200	204	199	184	192	187	197	187	182	185	189	172
641	202	245	305	314	321	301	295	316	308	322	307	302	292	277
648*	180	232	235	232	252									
684	162	161	218	222	222	203	217	217	210	214	206	211	197	186
686	173	191	211	210	223	198	194	192	186	189	187	196	192	180
689	180	213	235	249	279	250	222	201	203	202	186	193	176	172
690	214	299	303	331	302	258	251	249	244	259	262	239	227	207
699	198	238	235	230	242	212	218	226	228	248	244	242	257	293
726*	183	231	240	236	245									
Mean	195.3	225.9	242.9	257.5	254.3	245.5	243.9	238.2	236.1	240.9	237.1	237.1	236.3	223.2
Std Dev	27.8	44.4	37.8	42.4	44.0	43.4	40.4	40.9	38.5	42.6	43.7	40.7	51.2	46.0
SEM	7.2	11.5	9.8	11.0	11.4	13.7	12.8	12.9	12.2	13.5	13.8	12.9	16.2	14.5

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 6 Males

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
523*	187	138	147	171	208									
552*	194	112	189	178	191									
563	279	277	267	286	280	267	260	278	279	238	266	254	262	244
565	201	191	217	283	260	239	238	239	246	238	223	221	210	208
568	243	217	304	330	372	342	353	347	326	329	328	312	274	283
587*	178	211	219	210	223									
607	130	232	253	252	267	251	252	232	235	221	244	231	235	210
630	212	245	285	281	293	269	283	289	276	290	304	302	282	292
631*	185	210	228	222	245									
652	224	277	299	330	379	367	378	398	411	367	375	379	375	371
659	187	178	229	289	263	230	225	224	230	214	221	217	221	214
674*	193	145	171	218	232									
679	201	191	244	266	265	249	230	230	231	217	225	221	223	209
708	308	313	340	369	366	330	343	357	335	307	332	311	312	284
728	192	164	191	213	164	237	220	207	236	238	241	233	221	216
Mean	207.6	206.7	238.9	259.9	267.2	278.1	278.2	280.1	280.5	265.9	275.9	268.1	261.5	253.1
Std Dev	42.8	56.1	53.5	57.8	64.3	49.4	58.6	66.1	59.9	53.7	55.0	54.8	51.8	53.8
SEM	11.1	14.5	13.8	14.9	16.6	15.6	18.5	20.9	19.0	17.0	17.4	17.3	16.4	17.0

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 1 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
765*	193	184	174	162	178									
768	276	240	233	299	200	271	298	275	218	298	259	273	spill	233
772	157	143	137	141	146	150	158	160	166	154	141	155	160	160
776	180	180	168	166	135	182	148	135	143	115	146	124	143	144
778	201	212	206	211	209	222	211	209	219	217	192	200	244	217
806	195	210	179	171	164	190	166	153	150	139	141	156	172	187
810	195	209	223	237	208	227	222	251	182	256	214	247	252	269
814*	199	188	198	188	194									
815*	204	212	227	219	202									
818	166	193	182	169	222	197	163	171	194	188	178	166	179	176
825*	181	188	207	217	208									
832*	192	212	192	176	182									
833	177	167	173	173	185	179	175	194	182	193	181	154	201	198
843	198	197	205	232	223	247	215	221	218	217	192	198	213	219
849	165	231	219	249	275	275	239	285	256	268	206	308	297	320
Mean	191.9	197.7	194.9	200.7	195.4	214.0	199.5	205.4	192.8	204.5	185.0	198.1	206.8	212.3
Std Dev	27.4	24.5	26.3	42.0	33.8	41.5	46.6	52.3	35.3	58.7	37.0	59.8	49.8	52.6
SEM	7.1	6.3	6.8	10.8	8.7	13.1	14.7	16.5	11.2	18.6	11.7	18.9	16.6	16.6

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 2 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
752	141	141	137	166	147	167	160	177	156	159	160	149	169	spill
755	187	210	207	209	225	230	220	230	225	234	197	211	261	310
758*	290	289	275	315	285									
764	205	232	255	232	293	316	303	340	259	271	293	286	278	284
774	266	284	288	263	245	257	274	258	247	242	254	245	241	274
781*	184	206	208	203	186									
795	278	258	279	spill	229	spill	spill	349	440	69&	315	spill	spill	280
799*	203	255	280	spill	251									
804	206	213	215	257	195	209	222	218	203	204	187	173	210	212
829*	153	174	165	169	158									
837*	178	184	193	215	178									
838	146	145	146	180	187	215	220	240	239	253	237	237	284	274
840	222	217	217	214	202	233	218	218	210	202	193	179	219	216
850	166	210	228	226	208	224	220	275	272	253	234	244	278	spill
855	152	174	175	173	175	179	210	208	207	206	182	178	224	217
Mean	198.5	212.8	217.9	217.1	210.9	225.6	227.4	251.3	245.8	224.9	225.2	211.3	240.4	258.4
Std Dev	47.8	45.3	49.6	42.9	43.4	43.6	40.3	56.0	75.8	34.9	50.7	44.6	38.6	37.7
SEM	12.4	11.7	12.8	11.9	11.2	14.5	13.4	17.7	24.0	11.6	16.0	14.9	12.9	13.3

@ Quarantine week 2.
* Interim sacrifice animal.
& Value not considered reliable, not included in group mean.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 3 Females

Animal# 86D00-	QWK2[@]	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
749	194	206	spill	176	195	205	204	223	spill	190	178	158	207	179
751	231	250	256	261	262	315	279	284	297	302	293	213	337	spill
753	222	253	223	224	229	237	232	239	244	256	238	183	260	242
759*	183	190	169	145	161									
761	160	203	196	200	205	209	205	237	229	217	190	263	333	218
771*	212	194	158	166	172									
784	293	284	282	266	304	272	290	281	279	278	249	279	283	265
789*	182	203	196	spill	212									
802	187	179	210	212	209	262	228	240	187	185	184	167	252	231
803	220	341	314	363	353	334	340	304	spill	293	265	209	311	284
805	202	205	223	191	188	187	276	200	spill	168	173	145	180	178
826	216	212	spill	225	217	191	191	200	191	159	194	120	218	178
827	226	213	208	186	184	182	158	199	151	166	148	134	196	202
846*	234	260	240	268	236									
852*	173	173	168	176	188									
Mean	209.3	224.4	218.7	218.5	221.0	239.4	240.3	240.7	225.4	221.4	211.2	187.1	257.7	219.7
Std Dev	32.0	45.2	45.6	56.5	51.4	54.5	54.9	37.8	52.5	55.9	46.9	53.5	57.2	39.2
SEM	8.3	11.7	12.6	15.1	13.3	17.2	17.4	12.0	19.9	17.7	14.8	16.9	18.1	13.1

[@] Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 4 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
766	183	217	227	206	214	220	222	215	217	221	216	225	232	233
780	214	199	255	203	194	228	242	227	222	243	179	221	286	262
785*	260	301	322	344	299									
787	195	215	217	216	195	223	286	223	209	202	205	166	217	210
790*	238	263	270	275	244									
793	219	226	248	254	219	259	254	294	245	288	243	233	279	287
794*	225	262	264	235	180									
811	203	219	222	225	201	226	210	221	210	222	199	173	210	212
812	190	231	221	221	179	217	215	225	197	226	217	173	230	214
821*	187	221	217	291	197									
842*	169	192	165	167	165									
844	220	253	309	294	233	246	251	251	256	250	257	250	291	272
848	156	184	191	174	170	194	184	204	188	228	193	198	223	197
851	154	182	158	149	164	167	183	193	195	193	182	158	208	196
854	169	215	185	196	176	187	184	190	168	177	155	132	203	159
Mean	198.8	225.3	231.4	230.0	202.0	216.7	223.1	224.3	210.7	225.0	204.6	192.9	237.9	224.2
Std Dev	30.7	32.8	47.7	53.4	36.1	27.4	34.9	30.3	26.2	31.3	30.4	38.2	34.1	39.4
SEM	7.9	8.5	12.3	13.8	9.3	8.7	11.0	9.6	8.3	9.9	9.6	12.1	10.8	12.5

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 5 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
760	158	178	178	205	184	195	248	227	199	186	176	138	185	spill
762	182	221	208	215	spill	236	232	229	197	219	205	184	240	223
769	206	246	240	207	229	235	204	189	170	206	182	136	210	183
770	178	224	203	237	215	228	213	251	217	222	191	158	196	185
775*	149	182	171	161	154									
782*	213	246	226	215	206									
797*	213	209	231	262	233									
819	196	215	213	207	202	203	180	201	179	207	204	164	215	210
820	192	201	193	188	204	203	166	173	192	164	139	122	170	180
831	210	192	227	228	226	225	222	232	213	224	206	209	242	236
835*	205	213	224	234	197									
841*	174	199	209	197	200									
845	198	224	206	237	237	227	253	256	243	246	227	204	239	226
847	202	228	245	244	243	255	244	251	239	256	233	212	250	245
856	188	245	212	266	210	232	227	205	223	216	188	177	231	208
Mean	190.9	214.9	212.4	220.2	210.0	223.9	218.9	221.4	207.2	214.6	195.1	170.4	217.8	210.7
Std Dev	19.5	21.8	20.9	28.0	23.5	18.4	28.8	28.3	24.2	26.6	26.9	32.2	27.2	23.9
SEM	5.0	5.6	5.4	7.2	6.3	5.8	9.1	9.0	7.6	8.4	8.5	10.2	8.6	8.0

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix J (cont.): WATER CONSUMPTION (ml/week)

Group 6 Females

Animal# 86D00-	QWK2@	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
750	169	spill	171	200	188	195	197	200	181	178	180	162	235	202
754*	195	191	198	216	211									
757*	160	172	170	210	204									
773*	157	201	201	206	205									
779*	216	234	274	250	263									
783	251	327	316	334	295	316	288	304	265	304	279	295	333	340
792	139	152	169	178	202	185	182	189	155	184	173	161	207	189
798	192	193	218	254	260	243	273	269	282	273	254	231	289	260
809	205	262	227	277	298	305	312	313	286	302	273	270	338	282
813	207	229	252	245	213	288	217	242	286	205	192	204	223	237
816	192	184	191	211	225	237	238	276	241	214	201	spill	224	220
817	177	202	203	241	225	219	274	249	245	233	209	198	256	257
822	175	181	180	196	186	217	227	219	245	213	201	116	222	212
830	181	185	191	213	211	209	217	208	191	194	187	154	198	201
839*	149	162	151	163	157									
Mean	184.3	205.4	207.5	226.3	222.9	241.4	242.5	246.9	237.7	230.0	214.9	199.0	252.5	240.0
Std Dev	28.8	45.6	44.3	42.4	39.9	46.3	42.3	43.3	46.8	46.9	39.0	58.1	50.7	46.2
SEM	7.4	12.2	11.5	11.0	10.3	14.6	13.4	13.7	14.8	14.8	12.3	19.4	16.0	14.6

@ Quarantine week 2.
* Interim sacrifice animal.

Appendix K: BODY WEIGHTS (g)

Group 1 Males

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
530	133	175	182	243	302	337	372	395	426	454	474	491	502	513	524	537	550
539	103	97	97	176	240	284	316	337	354	371	389	405	417	448	459	482	491
543*	130	73	99	189	264	292	320	393									
557	132	196	201	264	330	375	412	437	466	493	516	532	535	545	560	573	581
566	122	95	124	205	274	323	360	392	420	452	473	496	521	536	552	571	593
577	151	176	208	287	355	403	441	471	493	528	541	559	573	592	604	619	632
618	110	147	151	205	284	329	363	389	417	448	479	500	510	525	545	553	559
620*	104	153	159	223	275	318	356	380									
635	114	171	179	224	283	335	367	395	421	446	464	489	504	523	539	553	559
680*	140	190	195	239	314	348	380	408									
681*	118	76	105	172	237	282	326	368									
688	107	156	165	214	260	290	313	342	356	380	398	409	423	435	450	458	472
706	104	153	160	221	279	308	341	363	381	396	410	425	436	452	459	464	475
707	134	192	202	258	311	334	350	371	391	410	423	449	458	489	504	511	523
712*	124	187	190	255	301	333	359	382									
Mean	122	149	161	225	287	326	358	388	413	438	457	476	488	506	520	532	544
Std Dev	15	43	39	33	32	33	35	34	44	50	51	52	52	50	51	52	53
SEM	4	11	10	9	8	9	9	9	14	16	16	16	16	16	16	17	17

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 2 Males

Animal# 86D00-	RPT[@]	ALC[$]	QWK1[†]	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
506*	135	101	128	203	278	326	363	399									
507*	115	184	191	262	315	355	399	424									
531	109	83	87	167	227	274	311	348	374	402	421	438	464	489	494	504	524
548*	127	99	187	247	287	320	349	373									
600	126	178	190	249	299	340	382	413	439	463	495	520	536	560	571	592	556
606*	133	96	94	174	254	309	339	388									
625	112	173	179	244	296	335	350	389	407	433	470	483	492	517	533	548	563
628	110	147	152	229	285	332	365	398	417	436	451	477	484	511	523	525	414
634	115	167	171	227	288	333	363	393	411	434	469	469	479	490	494	502	516
666	119	174	173	250	295	325	363	395	413	436	451	465	487	498	495	514	514
678	131	175	182	219	299	337	374	399	424	451	472	485	499	498	517	523	539
694	103	163	172	245	304	345	377	404	427	448	468	485	503	520	533	535	548
731	125	185	191	261	315	356	385	407	421	452	466	484	501	510	523	522	524
733*	115	169	174	237	286	329	361	385									
734	111	166	170	233	279	317	352	374	402	430	443	462	478	490	511	517	519
Mean	119	151	163	230	287	329	362	393	414	439	461	477	492	508	519	528	522
Std Dev	10	36	34	29	23	20	21	18	17	17	20	21	20	21	24	26	42
SEM	3	9	9	7	6	5	5	5	6	5	6	7	6	7	7	8	13

[@] Receipt.
[$] Allocation.
[†] Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 3 Males

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
510*	113	102	133	216	287	348	399	440									
511	139	111	158	225	284	325	363	383	418	434	450	470	484	499	507	512	525
520*	120	104	135	212	278	338	394	437									
526	110	149	158	204	253	281	311	330	350	362	381	394	406	407	413	425	433
544	124	136	135	214	276	320	355	382	406	428	449	468	481	498	516	530	544
553	132	186	193	250	314	354	390	420	441	470	491	512	531	553	565	582	601
581	108	73	95	153	222	248	313	352	393	424	452	480	498	521	530	542	561
583	132	190	202	268	318	366	398	428	466	496	521	548	560	584	612	635	653
599*	107	158	165	219	264	315	342	369									
602*	113	122	124	193	252	294	329	360									
696	107	163	178	236	282	311	341	366	388	406	426	443	455	473	491	489	513
698	108	169	175	241	284	320	354	377	402	425	437	458	474	493	505	509	527
713*	116	178	185	229	308	359	390	427									
717	125	184	191	262	324	364	378	431	458	478	501	516	518	542	551	555	574
723	107	82	85	153	218	270	307	343	372	394	417	442	460	480	493	503	514
Mean	117	140	154	218	278	321	358	390	409	432	453	473	487	505	518	528	545
Std Dev	11	39	35	34	32	36	33	37	37	41	42	44	43	49	53	56	59
SEM	3	10	9	9	8	9	9	10	12	13	13	14	14	16	17	18	19

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 4 Males

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
554*	124	184	189	253	298	345	380	408									
593*	134	195	208	276	323	365	398	430									
604*	137	193	200	264	315	354	393	425									
612	136	203	207	266	342	405	453	490	523	548	564	597	625	660	664	703	702
626	119	89	111	175	242	291	329	367	399	422	453	483	492	512	529	547	561
636	109	79	84	165	217	264	293	325	355	378	392	425	434	456	467	477	499
639	129	195	207	268	319	356	379	401	433	452	468	490	498	520	520	532	552
644*	107	91	97	171	247	293	339	374									
645*	122	180	184	246	297	333	369	399									
646	107	159	166	231	288	335	375	409	439	452	473	496	510	527	542	556	571
655	105	118	114	182	238	275	303	339	363	379	403	428	442	463	470	484	517
675	117	92	119	185	232	276	318	350	380	397	419	438	451	474	482	484	497
676	107	170	177	245	296	345	388	421	447	460	490	510	525	548	557	564	574
703	117	177	180	239	284	326	363	387	416	433	450	474	487	502	511	524	530
718	114	162	168	228	271	310	345	371	403	417	432	450	471	492	494	509	516
Mean	119	152	161	226	281	325	362	393	416	434	454	479	494	515	524	538	552
Std Dev	11	45	43	40	38	39	42	42	49	50	50	51	55	59	58	66	60
SEM	3	12	11	10	10	10	11	11	15	16	16	16	17	19	18	21	19

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 5 Males

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
509*	115	90	95	166	211	258	301	332									
533*	113	85	91	165	202	260	303	338									
550	113	82	90	162	205	248	290	322	346	363	381	402	426	439	458	471	485
570	118	144	187	255	303	348	392	425	457	487	511	533	556	575	598	609	621
617	128	179	189	249	293	337	369	391	416	443	458	479	488	511	520	536	543
621*	113	77	78	151	211	265	309	345									
632	107	158	161	214	258	295	324	347	368	387	402	424	437	454	461	469	473
641	129	93	117	200	251	313	354	389	430	460	491	515	534	555	568	579	595
648*	125	171	173	213	279	328	365	394									
684	105	81	84	153	184	241	278	312	338	366	392	412	431	453	466	480	492
686	112	168	167	227	262	301	328	361	389	412	429	452	454	460	482	492	496
689	117	174	180	251	299	352	394	432	464	489	501	525	538	550	563	570	585
690	114	88	87	154	214	269	309	344	373	399	421	452	472	495	506	527	542
699	134	187	200	239	295	341	380	406	452	451	472	494	515	537	546	561	562
726*	107	167	173	242	293	344	382	404									
Mean	117	130	138	203	251	300	339	369	403	426	446	469	485	503	517	529	539
Std Dev	9	44	47	40	42	40	40	38	47	47	47	48	48	50	50	50	51
SEM	2	11	12	10	11	10	10	10	15	15	15	15	15	16	16	16	16

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 6 Males

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
523*	126	93	95	171	189	230	278	314									
552*	116	155	162	219	215	256	290	322									
563	115	91	114	454&	223	273	319	365	402	431	454	485	507	528	544	559	571
565	108	162	169	224	240	276	321	350	384	403	421	442	460	472	489	496	508
568	113	175	179	228	247	303	348	387	426	452	472	501	515	539	564	580	601
587*	108	164	174	230	257	296	328	353									
607	143	195	204	268	305	350	389	415	456	474	491	518	534	560	578	588	601
630	118	163	169	229	255	298	343	374	399	426	443	470	491	510	529	541	555
631*	107	167	172	231	239	278	323	359									
652	106	160	154	210	229	264	304	329	362	387	399	412	431	442	454	461	471
659	104	106	106	165	195	238	285	316	344	364	383	402	420	436	452	460	472
674*	114	168	172	202	228	262	315	354									
679	141	189	197	253	299	349	385	413	421	461	478	499	516	536	546	563	575
708	135	193	196	265	277	323	365	397	425	452	474	484	494	515	524	543	555
728	110	160	164	224	245	281	321	347	373	395	403	422	446	465	474	481	495
Mean	118	156	162	223	243	285	328	360	399	425	442	464	481	500	515	527	540
Std Dev	13	33	33	30	33	36	33	33	34	36	38	41	39	43	45	49	50
SEM	3	9	8	8	9	9	9	8	11	11	12	13	12	14	14	15	16

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.
& Not included in group mean.

Appendix K (cont.): BODY WEIGHTS (g)

Group 1 Females

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
765*	120	178	184	214	238	248	253	276									
768	109	146	152	174	182	206	208	222	228	238	242	254	239	256	259	272	275
772	109	150	156	177	190	190	199	207	217	222	230	234	245	235	242	248	255
776	109	147	157	177	202	220	231	219	240	242	247	255	247	262	254	267	262
778	114	155	169	196	227	241	248	262	278	283	283	293	297	303	297	310	310
806	112	164	172	207	238	241	257	261	275	282	282	281	280	287	286	297	299
810	114	154	166	192	223	240	256	251	264	266	281	276	282	291	283	298	302
814*	106	161	181	203	209	226	236	242									
815*	103	148	161	191	220	240	249	252									
818	116	160	172	194	228	237	253	289	284	292	286	298	299	305	303	309	307
825*	116	162	168	183	206	222	233	241									
832*	111	151	166	183	209	231	239	246									
833	124	173	174	207	220	236	239	266	272	274	282	282	289	292	288	299	313
843	123	169	184	218	237	261	272	284	302	308	313	323	328	335	333	343	347
849	131	175	173	196	223	240	248	263	283	283	298	314	317	320	322	338	348
Mean	114	160	169	194	217	232	241	252	264	269	274	281	282	289	287	298	302
Std Dev	7	11	10	14	17	17	19	24	27	27	26	28	30	30	29	30	31
SEM	2	3	3	4	4	4	5	6	9	9	8	9	10	10	9	9	10

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 2 Females

Animal# 86D00-	RPT[@]	ALC[$]	QWK1[†]	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
752	108	148	157	191	211	214	236	245	257	252	268	270	277	282	284	294	289
755	110	150	162	195	213	239	250	269	279	281	287	285	304	299	290	295	291
758*	111	172	180	225	252	280	306	325									
764	114	162	172	200	222	244	252	269	287	288	301	300	301	309	314	329	337
774	112	160	175	211	232	270	286	288	295	330	339	340	338	362	364	356	361
781*	122	164	173	205	240	254	277	277									
795	119	152	166	208	235	267	265	284	311	347	346	342	397	405	400	416	428
799*	117	160	171	192	220	240	255	249									
804	121	173	179	224	237	253	278	272	294	303	314	332	332	347	329	344	346
829*	105	138	150	171	191	207	220	231									
837*	96	147	159	192	211	224	246	245									
838	113	155	156	178	195	199	204	216	230	229	233	248	264	260	261	278	279
840	127	175	191	223	239	267	296	301	315	335	348	352	356	375	367	387	395
850	108	150	157	179	194	211	219	232	247	249	251	260	275	269	270	279	295
855	114	163	169	202	222	236	242	259	269	274	291	301	310	303	304	323	331
Mean	113	158	168	200	221	240	255	264	278	289	298	303	315	321	318	330	335
Std Dev	8	11	11	17	18	25	29	29	28	40	40	37	41	49	46	46	49
SEM	2	3	3	4	5	7	8	7	9	13	13	12	13	15	15	15	16

[@] Receipt.
[$] Allocation.
[†] Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 3 Females

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
749	122	164	167	193	206	218	222	234	248	252	255	265	269	268	264	279	278
751	121	175	188	212	244	265	277	283	307	309	315	320	335	352	334	351	339
753	94	146	156	182	214	234	249	246	266	278	288	288	305	321	292	313	315
759*	113	157	169	198	222	238	242	253									
761	117	155	165	179	212	235	251	258	278	276	287	300	308	309	340	359	345
771*	110	165	180	214	226	233	245	267									
784	109	174	195	229	259	286	289	304	325	329	334	352	360	365	367	376	381
789*	123	164	171	215	238	264	273	295									
802	123	179	196	215	227	265	280	285	313	312	333	328	341	341	334	356	359
803	116	171	188	265	258	292	312	316	349	364	386	392	410	422	407	431	443
805	113	155	162	200	210	238	251	257	266	261	274	288	283	299	290	305	305
826	117	167	179	220	240	274	301	308	312	332	315	325	337	347	325	348	346
827	113	159	177	192	233	248	263	263	277	266	263	283	289	292	282	296	307
846*	98	148	160	208	238	266	281	287									
852*	105	149	154	172	209	221	232	251									
Mean	113	162	174	206	229	252	265	274	294	298	305	314	324	332	324	341	342
Std Dev	9	10	14	23	17	23	26	25	32	37	40	38	42	44	43	45	47
SEM	2	3	4	6	4	6	7	6	10	12	13	12	13	14	14	14	15

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 4 Females

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
766	99	141	146	171	198	213	221	236	251	254	258	267	277	276	289	287	298
780	111	154	166	177	209	226	241	249	265	267	279	286	290	294	289	318	331
785*	105	153	168	213	244	278	293	315									
787	124	166	168	183	212	233	256	250	277	278	289	294	289	309	297	310	318
790*	121	171	185	209	248	269	302	316									
793	123	175	187	211	233	250	271	283	297	311	319	323	321	324	327	340	347
794*	124	170	175	219	239	264	281	276									
811	119	155	162	185	220	240	253	253	270	275	283	282	287	294	285	296	297
812	118	172	186	209	242	266	288	280	306	314	329	328	340	346	336	349	351
821*	108	159	170	186	216	231	246	257									
842*	121	162	173	205	222	226	250	260									
844	125	167	176	205	222	242	265	273	276	287	290	300	306	314	304	306	308
848	112	156	160	192	206	234	252	259	270	280	290	299	310	313	304	316	316
851	106	147	152	178	202	218	231	245	249	261	263	280	279	285	271	287	291
854	102	149	157	185	208	229	238	243	267	270	277	283	287	293	286	296	291
Mean	115	160	169	195	221	241	259	266	273	280	288	294	299	305	299	311	315
Std Dev	9	10	12	16	16	20	24	24	18	20	22	19	20	21	20	21	22
SEM	2	3	3	4	4	5	6	6	6	6	7	6	6	7	6	7	7

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 5 Females

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
760	114	172	183	189	222	240	276	270	281	278	294	293	301	295	289	297	301
762	120	160	168	193	208	232	256	260	268	276	288	283	289	295	286	308	304
769	124	168	181	206	234	254	264	284	302	312	326	319	327	339	327	337	339
770	120	170	184	200	240	251	288	295	322	315	344	346	360	354	343	346	351
775*	111	163	169	190	226	251	263	271									
782*	123	167	178	208	239	264	277	287									
797*	118	171	178	222	242	272	323	321									
819	103	159	179	212	247	280	299	296	318	319	335	321	344	345	338	352	351
820	112	170	175	209	230	238	241	265	279	276	279	298	306	300	290	299	306
831	116	163	174	204	213	237	254	264	278	285	297	297	305	303	308	317	319
835*	118	156	168	198	216	231	247	258									
841*	110	152	162	183	200	215	225	239									
845	103	153	167	204	235	256	272	287	294	322	328	331	335	345	359	361	361
847	121	174	184	230	240	269	288	297	316	317	337	329	342	349	341	355	358
856	107	138	150	177	210	223	249	250	265	270	281	286	292	289	295	313	302
Mean	115	162	173	202	227	248	268	276	292	297	311	310	320	321	318	329	329
Std Dev	7	10	9	14	15	19	25	22	21	22	25	22	25	27	27	24	25
SEM	2	3	2	4	4	5	6	6	7	7	8	7	8	8	9	8	8

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix K (cont.): BODY WEIGHTS (g)

Group 6 Females

Animal# 86D00-	RPT@	ALC$	QWK1†	WK0	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12	WK13
750	112	159	174	215	220	242	268	280	295	301	318	320	329	341	326	341	345
754*	99	163	173	194	198	226	241	263									
757*	110	166	172	193	205	218	239	261									
773*	121	167	178	201	215	240	262	278									
779*	116	164	173	214	214	241	251	289									
783	128	172	190	220	241	264	280	281	311	316	330	322	325	328	337	356	357
792	107	150	162	188	184	201	220	232	241	247	257	254	262	269	264	265	276
798	126	174	181	217	216	226	246	263	272	294	294	317	325	330	326	338	338
809	91	142	157	195	206	237	263	291	311	317	335	341	356	362	359	379	380
813	115	161	171	208	216	239	258	270	274	273	294	302	308	305	317	325	331
816	109	155	161	188	194	213	227	247	259	268	280	291	292	291	288	305	304
817	122	173	186	216	201	229	250	264	268	290	301	316	320	315	322	329	340
822	107	156	169	193	198	219	233	235	253	263	274	268	274	281	269	284	279
830	123	169	175	205	219	246	267	276	288	294	314	315	311	319	315	339	332
839*	111	147	155	175	181	191	211	206									
Mean	113	161	172	201	207	229	248	262	277	286	300	305	310	314	312	326	328
Std Dev	10	10	10	13	15	19	19	24	24	23	25	27	28	28	30	34	33
SEM	3	3	3	3	4	5	5	6	8	7	8	8	9	9	9	11	10

@ Receipt.
$ Allocation.
† Quarantine week 1.
* Interim sacrifice animal.

Appendix L: INDIVIDUAL ANIMAL HISTORIES

MALE: 0 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00707	Irritable	Nov 27-Dec 1	
		Dec 29,Jan 5,6,8,9	
		Jan 11,12,14-16	
		Jan 23-30,Feb 2	Moderate
86D00706	Chromodacryorrhea	Nov 12	Slight
	Irritable	Nov 12,13,19,20	
		Dec 11,23,29	
		Jan 6,28-30	Moderate
	Incr. Startle Reflex	Nov 14	Slight
86D00688	Incr. Startle Reflex	Nov 13	Slight
	Irritable	Nov 17,21,24	
		Dec 17,23,Jan 28	Slight
	Stain, Red, Nose	Jan 30	Slight
86D00635	Irritable	Jan 11,12	Slight
	Stain, Red, Nose	Jan 21	Moderate
86D00618	Material, Red, Nose	Dec 17	Slight
	Aggressive	Dec 27,28,Jan 5	
		Jan 14,15	Moderate
	Irritable	Dec 29,Jan 3,22	
		Jan 26,27	Moderate
	Stain, Red, Nose	Jan 4,10-12	Moderate
86D00577	Material, Red, Nose	Dec 17,Feb 4	Slight
	Irritable	Dec 23,29,30,Jan 21	
		Jan 28	Moderate
	Stain, Red, Nose	Jan 28	Slight
	Material, Dark, Nose	Feb 2,3	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 0 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00566	Stain, Red, Nose	Dec 13,Jan 3-6,14	Slight
	Rough Coat	Jan 14-24	
		Jan 30-Feb 2	Moderate
	Irritable	Jan 30	Slight
86D00557	Material, Red, Nose	Dec 3	Slight
	Irritable	Dec 17,18,29,30	
		Jan 4,28,30	Moderate
	Material, Dark, Nose	Dec 24,26,27	Moderate
	Stain, Red, Nose	Jan 4	Slight
86D00539	Irritable	Dec 24,Jan 1,5,6	
		Jan 9,10,22-25	
		Jan 28-30	Moderate
	Stain, Red, Nose	Jan 9,14	Slight
	Material, Red, Nose	Jan 29	Slight
86D00530	Irritable	Nov 21,Dec 9	
		Jan 4,5,8,9,12,22-25	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
MALE: 0 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00543	Normal	N/A	N/A
86D00620	Irritable	Nov 12,18,25	Moderate
86D00680	Irritable	Nov 20,21,29,30	Slight
	Stain, Orange, Abdomen	Nov 27,28	Slight
86D00681	Normal	N/A	N/A
86D00712	Normal	N/A	N/A

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 1 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00531	Irritable	Dec 25-28	Moderate
	Alopecia, Front Legs	Jan 29,Feb 1,2	Slight
	Stain, Brown, Front Leg	Feb 2	Slight
86D00600	Irritable	Nov 13,17,Dec 2	
		Dec 14,15,24	
		Dec 30-Jan 5	
		Jan 13-16,22-25	Moderate
	Incr. Startle Reflex	Dec 24,25	Moderate
	Material, Dark, Nose	Dec 28,29	Slight
	Stain, Red, Nose	Jan 2-5,9	Slight
	Alopecia, Hind Legs	Jan 17-21	Slight
	Rough Coat	Jan 19-21	Slight
	Aggressive	Jan 26,29,30	Slight
86D00625	Stain, Red, Nose	Feb 1	Moderate
86D00628	Material, Red, Nose	Nov 17	Slight
	Irritable	Dec 24,Jan 5-7	
		Jan 11,22	Moderate
	Material, Dark, Nose	Dec 22,26	Slight
	Stain, Red, Nose	Jan 4,14	Slight
	Stain, Red, Front Legs	Jan 10,11	Slight
	Stain, Dark, Nose	Jan 29-31	Moderate
	Rough Coat	Feb 1,2	Slight
	Stain, Brown, Nose	Feb 2	Slight
86D00634	Irritable	Nov 17,Dec 11	
		Jan 1,7,Feb 5	Moderate
86D00666	Incr. Startle Reflex	Nov 14	Slight
	Alopecia, Front Legs	Dec 24-Feb 4	Marked
	Irritable	Jan 11	Slight
	Alopecia, Hind Legs	Jan 17-Feb 3	Slight
86D00678	Irritable	Nov 17,Jan 8,29	Slight
	Material, Dark, Nose	Dec 25,27	Slight
	Stain, Red, Nose	Jan 4,9,10,21,22	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 1 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00694	Irritable	Nov 20,21,Dec 11	
		Jan 5,6,8,12,13,21	Slight
86D00731	Irritable	Nov 12,18,Dec 29,30	
		Jan 1,Feb 3	Moderate
	Stain, Red, Nose	Jan 4	Slight
	Material, Dark, Nose	Jan 22	Slight
86D00734	Irritable	Nov 14,Dec 2,24	
		Jan 27,28	
		Feb 3,4,5	Moderate
	Material, Red, Nose	Jan 23	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
MALE: 1 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

86D00506	Normal	N/A	N/A
86D00507	Stain, Red, Nose	Nov 27,28	Slight
86D00548	Material, Dark, Nose	Nov 24	Slight
86D00606	Incr. Startle Reflex	Nov 14	Slight
86D00733	Irritable	Nov 20,21	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 10 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00511	Irritable	Dec 16,Jan 4,6,13	Slight
	Material, Dark, Nose	Dec 22,Jan 23	Slight
	Stain, Red, Nose	Jan 11	Slight
86D00526	Irritable	Jan 1	Slight
	Stain, Red, Nose	Jan 8	Slight
	Stain, Red, Mouth	Jan 8	Slight
86D00544	Material, Red, Nose	Nov 24,Jan 1,4	
		Jan 5,7,10	Slight
	Stain, Red, Back	Dec 24	Moderate
	Irritable	Jan 6,9	Slight
	Material, Dark, Nose	Jan 23	Slight
	Material, Brown, Nose	Feb 1	Slight
86D00553	Irritable	Nov 12,14,Dec 17	
		Jan 3,11	Marked
	Rough Coat	Dec 17-23,25-28	
		Jan 9-14,18-Feb 3	Slight
	Aggressive	Dec 28,Jan 26-30	Moderate
	Stain, Red, Nose	Jan 4,8,26	Slight
86D00581	Incr. Startle Reflex	Nov 13,Jan 3,4	Slight
	Irritable	Jan 4	Slight
86D00583	Incr. Startle Reflex	Nov 13	Slight
	Feces, Brown, Perianal	Nov 27	Slight
	Material, Red, Nose	Dec 17,29	Slight
	Irritable	Jan 5,8,9,11,14	
		Jan 15,28,29	
		Feb 1-3	Moderate
	Aggressive	Jan 7	Slight
	Alopecia, Front Legs	Jan 11-Feb 3	Slight
	Stain, Red, Front Legs	Jan 11	Slight
	Stain, Red, Nose	Jan 26	Slight
	Material, Dark, Nose	Jan 30	Slight
	Stain, Brown, Front Legs	Jan 30-Feb 1	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 10 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00696	Irritable	Nov 12,17,19-21	
		Dec 5,15,16,22-24	
		Dec 29,30,Jan 1-4	
		Jan 6,8,9,12-16	Moderate
	Stain, Red, Nose	Jan 10,31	Moderate
86D00698	Material, Dark, Nose	Dec 17	Slight
	Irritable	Jan 1	Slight
86D00717	Incr. Startle Reflex	Nov 12,19,20	
		Dec 24-27	Slight
	Material, Red, Nose	Dec 3,11,25,29	
		Jan 22	Slight
	Material, Dark, Nose	Dec 17-23,Jan 30	Slight
	Irritable	Jan 2-6,11,13	Moderate
	Stain, Red, Nose	Jan 4,5,14,15,26	Moderate
	Stain, Dark, Nose	Jan 8-10	Slight
86D00723	Irritable	Nov 17,18,Dec 12	
		Jan 1,4-6,26,27,29	Moderate
	Material, Red, Nose	Nov 27,28	Slight
	Incr. Startle Reflex	Dec 24,Jan 1	Slight
	Aggressive	Dec 28	Slight
	Stain, Red, Nose	Jan 4,9,10,14	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28 DAY (INTERIM SACRIFICE)
MALE: 10 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

86D00510	Normal	N/A	N/A
86D00520	Irritable	Nov 20	Slight
86D00599	Inactive	Nov 6	Slight
86D00602	Normal	N/A	N/A
86D00713	Normal	N/A	N/A

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00612	Material, Red, Nose	Nov 13	Slight
	Incr. Startle Reflex	Nov 13	
		Dec 29-Jan 1	Moderate
	Irritable	Nov 13,14	
		Dec 3-5,11-13	
		Dec 22-25,27-29	
		Jan 1-3,6,8-16	
		Jan 21,22,31	Marked
	Material, Dark, Nose	Dec 18,22	Slight
	Aggressive	Dec 18,26,27	
		Jan 23-30,Feb 2	Moderate
	Stain, Red, Back	Dec 24	Slight
	Stain, Red, Nose	Jan 4,9-11	Slight
	Rough Coat	Jan 11	Slight
86D00626	Material, Red, Nose	Nov 13,Dec 26	Slight
	Irritable	Nov 13,Dec 23,24	
		Dec 29-31,Jan 11,28	Marked
	Material, Dark, Nose	Dec 22,Jan 26,27	Slight
	Stain, Red, Nose	Jan 1,29	Slight
	Aggressive	Jan 26,27	Slight
86D00636	Incr. Startle Reflex	Nov 12	Slight
	Aggressive	Dec 26	Slight
	Stain, Red, Nose	Jan 18,30,31	Slight
	Material, Dark, Nose	Jan 26,27	Slight
	Irritable	Jan 28	Slight
	Stain, Brown, Nose	Feb 2	Slight
86D00639	Irritable	Dec 3,29	
		Jan 21,22,29,30	
		Feb 2	Moderate
	Incr. Startle Reflex	Dec 28,29	
		Jan 17	Moderate

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00646	Incr. Startle Reflex	Nov 12	Slight
	Irritable	Dec 23,29-31	
		Jan 5,6	Moderate
	Aggressive	Dec 28	Slight
	Stain, Red, Front Leg	Jan 1,10,11,14-21	Slight
86D00655	Irritable	Dec 28,29,Jan 6,7	
		Jan 11,28,Feb 1	Moderate
	Stain, Red, Nose	Jan 19,20	Moderate
86D00675	Incr. Startle Reflex	Nov 12,13,21,22	
		Dec 24,25	Slight
	Irritable	Nov 12,Dec 23,24	
		Jan 6	Moderate
86D00676	Incr. Startle Reflex	Nov 13,21	Slight
	Material, Red, Nose	Nov 27	Slight
	Irritable	Jan 6	Slight
	Stain, Red, Nose	Jan 11,21,28	Moderate
86D00703	Incr. Startle Reflex	Nov 12,Dec 24-26	Slight
	Aggressive	Nov 12,19,21	
		Dec 18,24-28	
		Jan 23-30	Moderate
	Inactive	Nov 12	
	Irritable	Nov 13,20,Dec 11,12	
		Jan 4-6,9-12,16	Moderate
	Material, Red, Nose	Dec 19,20	Slight
86D00718	Irritable	Nov 12,13,Dec 29,30	
		Jan 3,4,10,12	Moderate
	Incr. Startle Reflex	Nov 13	Slight
	Aggressive	Dec 25-28	
		Jan 26-30,Feb 2,3	Moderate
	Stain, Red, Head	Jan 1	Slight
	Stain, Red, Back	Jan 10	Slight
	Stain, Red, Nose	Jan 11	Slight
	Stain, Red, Eye	Jan 11	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
MALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

86D00554	Normal	N/A	N/A
86D00593	Incr. Startle Reflex	Nov 12-14,18 Nov 20,21	Moderate
	Irritable	Nov 17,Dec 2	Slight
86D00604	Irritable	Nov 12,20	Slight
86D00644	Normal	N/A	N/A
86D00645	Normal	N/A	N/A

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00550	Incr. Startle Reflex	Nov 13,14,21	Slight
	Material, Dark, Nose	Dec 25	Slight
	Irritable	Jan 1,3,4,11,13	Slight
	Stain, Red, Nose	Jan 28	Slight
86D00570	Irritable	Nov 12,14,17,19,20	
		Nov 24-Dec 5,Dec 12	
		Dec 13,15,16,24,25	
		Jan 1-4,10-13,21-29	Moderate
	Incr. Startle Reflex	Nov 14,19,20,Dec 29	
		Dec 30,Jan 1,5-7	Moderate
	Stain, Brown, Nose	Ja 23	Moderate
	Stain, Red, Nose	Jan 26-28,30,31	Slight
86D00617	Incr. Startle Reflex	Nov 13,14,19	Slight
	Stain, Red, Nose	Jan 10,31	Slight
86D00632	Incr. Startle Reflex	Nov 14	Slight
	Material, Red, Nose	Dec 3	Slight
	Stain, Red, Nose	Jan 1,11,26-28	Slight
	Stain, Red, Neck	Jan 1,3	Moderate
	Irritable	Jan 4	Slight
	Aggressive	Jan 5	Slight
	Stain, Red, Ear	Jan 28-Feb 1	Slight
86D00641	Irritable	Nov 12,14-16	
		Jan 3-5,11	Slight
	Incr. Startle Reflex	Nov 14-16,20	
		Dec 25-28	
		Jan 21-23	Moderate
	Material, Brown, Nose	Jan 22	Slight
86D00684	Irritable	Nov 12,14-16	
		Dec 2,23,Feb 3	Slight
	Material, Red, Nose	Dec 1	Slight
	Material, Dark, Nose	Dec 25,26	Slight
	Stain, Red, Nose	Jan 26	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00686	Stain, Brown, Perianal	Nov 6	Slight
	Incr. Startle Reflex	Nov 14,19,Jan 4	Slight
	Hyperactive	Nov 14	
	Irritable	Nov 14,15,17	
		Jan 5	Slight
86D00689	Irritable	Nov 12,14-16	
		Dec 23	Slight
	Incr. Startle Reflex	Nov 14	Slight
	Material, Dark, Nose	Dec 22,Jan 26-30	Moderate
	Rough Coat	Jan 19-23,Feb 3	Slight
	Stain, Dark, Nose	Jan 21-23	Slight
	Stain, Red, Nose	Feb 4,5	Slight
86D00690	Incr. Startle Reflex	Nov 14,Jan 22	Slight
	Irritable	Nov 14-16,Dec 23	
		Jan 1	Slight
	Material, Red, Nose	Dec 28	Slight
	Stain, Red, Nose	Jan 18	Slight
	Rough Coat	Jan 19-21	Slight
	Material, Dark, Nose	Jan 22,23	Slight
86D00699	Irritable	Nov 11,12,14-Dec 5	
		Dec 9,11,12,23-25	
		Dec 29-Jan 1	
		Jan 5,6,8-16	
		Jan 20,21,31,Feb 1	Marked
	Incr. Startle Reflex	Nov 12,14,15,19-22	
		Dec 1,2,13,17-23	
		Dec 29,30,Jan 26,28	Marked
	Aggressive	Dec 22,26-28	
		Jan 7,22-30	
		Feb 3-5	Moderate
	Material, Red, Nose	Dec 25,26	Slight
	Rough Coat	Jan 17-19	Slight
	Material, Brown, Nose	Jan 30	Slight
	Stain, Red, Nose	Feb 4,5	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
MALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

86D00533	Irritable	Nov 12,14,17,Dec 2	Slight
	Incr. Startle Reflex	Nov 13,14	Moderate
	Stain, Brown, Perianal	Nov 14	Slight
86D00509	Incr. Startle Reflex	Nov 14,20,21	Slight
	Irritable	Nov 17,20,21,Dec 2	Slight
86D00621	Irritable	Nov 12,14,21,26	Slight
	Incr. Startle Reflex	Nov 14-16,20-22	Slight
86D00648	Irritable	Nov 12,Dec 2	Slight
	Incr. Startle Reflex	Nov 14	Slight
86D00726	Stain, Brown, Perianal	Nov 6	Slight
	Diarrhea	Nov 14	
	Incr. Startle Reflex	Nov 14,19,21	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00563	Irritable	Nov 5,Dec 15-19	
		Dec 24,Jan 1,3,6,7	
		Jan 10,11,13-16	Marked
	Rough Coat	Nov 11,12,15-17	
		Dec 14-16,26-28	
		Dec 30,Jan 6,7,9-11	
		Jan 14-20,28-Feb 1	Moderate
	Inactive	Nov 14	Slight
	Incr. Startle Reflex	Nov 20,21,Jan 1	Slight
	Stain, Red, Nose	Jan 3	Moderate
	Stain, Dark, Nose	Jan 21	Moderate
	Aggressive	Jan 28-30	Slight
86D00565	Rough Coat	Nov 12	Slight
	Material, Red, Nose	Nov 12	Slight
	Incr. Startle Reflex	Nov 14,15,Jan 1	Slight
	Irritable	Nov 19,21,Dec 2	
		Jan 7	Slight
	Material, Dark, Nose	Dec 25,Jan 30	Slight
	Stain, Red, Nose	Jan 28,31	Moderate
	Stain, Brown, Mouth	Jan 28	Slight
86D00568	Material, Red, Nose	Nov 12	Slight
	Incr. Startle Reflex	Nov 14-16,Jan 1	Slight
	Irritable	Dec 27,28	Slight
	Stain, Red, Nose	Jan 11	Slight
	Alopecia, Hind Legs	Jan 22-Feb 1	Slight
	Alopecia, Neck	Jan 28-Feb 1	Slight
	Aggressive	Jan 28-31	Slight
86D00607	Tremors	Nov 12	Slight
	Jumping	Nov 12	Slight
	Incr. Startle Reflex	Nov 13-18	Slight
	Irritable	Nov 17,18,Dec 29,30	
		Jan 6,11,30	Moderate
	Material, Red, Nose	Dec 3	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00630	Stain, Brown, Perianal	Nov 6,7	Slight
	Incr. Startle Reflex	Nov 17,18,Jan 30,31	Slight
	Material, Clear, Nose	Dec 3	Slight
	Alopecia, Front Legs	Jan 10-Feb 1	Moderate
	Rough Coat	Jan 17-20	Slight
	Stain, Red, Nose	Jan 28-30,Feb 4	Slight
86D00652	Jumping	Nov 12	Slight
	Incr. Startle Reflex	Nov 17,Jan 12	Slight
	Irritable	Jan 3,7,12	Slight
	Rough Coat	Jan 19,20	Slight
	Stain, Red, Nose	Jan 31	Moderate
86D00659	Incr. Startle Reflex	Nov 14,18,20	
		Dec 28	Slight
	Irritable	Nov 18,Jan 30	Slight
	Material, Red, Nose	Dec 6,15,Jan 6	Moderate
	Stain, Red, Nose	Jan 30,Feb 1	Slight
86D00679	Incr. Startle Reflex	Nov 14,20	Moderate
	Irritable	Nov 19,Dec 17-21	
		Jan 3-5,11,29	
		Feb 4,5	Slight
	Rough Coat	Nov 19-23	
		Jan 19-Feb 1	Slight
	Material, Red, Nose	Dec 17,24	Slight
	Stain, Yellow, Perianal	Dec 22,23	Slight
	Stain, Red, Nose	Jan 2,10	Slight
	Alopecia, Front Legs	Jan 17-Feb 1	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

MALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/1987)	Severity
86D00708	Material, Red, Nose	Nov 12,Dec 17,28	Slight
	Incr. Startle Reflex	Nov 13-15,17-20	
		Nov 24,Dec 29-Jan 4	
		Jan 26-30	Moderate
	Irritable	Nov 16,19,20,24-26	
		Jan 1	Slight
	Stain, Red, Nose	Jan 7,18,21,22,28	
		Feb 4	Marked
	Material, Dark, Nose	Jan 9,30,31	Moderate
	Stain, Red, Front Legs	Jan 18	Slight
86D00728	Jumping	Nov 12	Slight
	Incr. Startle Reflex	Nov 20,Jan 4	Moderate
	Irritable	Nov 20,Dec 1,3,5-8	
		Dec 29,30,Jan 10	
		Jan 13-15,26-29	Moderate

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
MALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

86D00523	Dehydrated	Nov 11,12	Moderate
	Rough Coat	Nov 11,12,27,28	Slight
	Jumping	Nov 12	Slight
	Emaciated	Nov 12-23	Slight
	Incr. Startle Reflex	Nov 14-16,19	Slight
	Irritable	Nov 17,18,Dec 2	Slight
86D00552	Dehydrated	Nov 11,12	Moderate
	Rough Coat	Nov 11-16	Moderate
	Irritable	Nov 11,18	Moderate
86D00587	Inactive	Nov 6	Slight
	Irritable	Nov 12,14-19,25,26	
		Dec 3	Slight
	Stain, Red, Mouth	Dec 1	Slight
86D00631	Inactive	Nov 6,7	Slight
	Incr. Startle Reflex	Nov 13-16	Slight
86D00674	Jumping	Nov 12	Slight
	Irritable	Nov 14-16,24-26	Slight
	Incr. Startle Reflex	Nov 20	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 0 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00768	Incr. Startle Reflex	Dec 16,17	
		Jan 8,21	Slight
	Irritable	Feb 12,Mar 7	Slight
86D00772	Stain, Red, Back	Dec 16,Jan 18,31	
		Feb 1	Moderate
	Incr. Startle Reflex	Dec 30	Slight
	Dehydrated	Dec 31	Slight
	Hair Clumped, Back	Jan 19	N/A
	Rough Coat	Jan 20-23,26-31	
		Feb 1-11	Moderate
	Stain, Red, Nose	Jan 29	Slight
	Material, Red, Nose	Mar 9	Slight
86D00776	Scab, R. Front Leg	Dec 14	Slight
	Scab, Back	Dec 22	Slight
	Alopecia, Back	Dec 23-28	Slight
	Alopecia, Front Legs	Jan 17-22	
		Feb 12-18	Moderate
	Stain, Red, Nose	Feb 3,6,7,21	Slight
	Stain, Brown, R. Front Leg	Feb 12-28	Slight
86D00778	Material, Red, Nose	Jan 30,Mar 9	Slight
86D00806	Stain, Red, Nose	Dec 17,Jan 23	
		Feb 21	Moderate
	Incr. Startle Reflex	Jan 8	Slight
	Irritable	Jan 23-28	
		Feb 7,8,13-19	
		Feb 21-24	Moderate
	Agressive	Jan 30,Feb 9	
		Mar 8,9	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 0 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00810	Scab, Neck	Dec 13,14	Slight
	Irritable	Dec 15,23	
		Jan 23,27,29,30	
		Feb 21-24,Mar 7,8	Moderate
	Alopecia, Neck	Dec 15-28	
	Alopecia, Front Legs	Jan 17-22,31-Feb 2	
		Mar 8-12	Slight
	Material, Red, Nose	Dec 27	Slight
	Incr. Startle Reflex	Jan 8,21,22	
		Feb 8,9	Slight
	Stain, Red, Nose	Jan 16,23,29	
		Feb 1,22	Moderate
	Material, Dark, Nose	Feb 21	Slight
86D00818	Stain, Red, Nose	Jan 27,31	Slight
	Incr. Startle Reflex	Jan 31,Feb 2	Marked
	Irritable	Feb 7,22,Mar 8	Moderate
	Material, Red, Nose	Feb 24	Slight
	Material, Dark, Nose	Feb 21	Slight
86D00833	Incr. Startle Reflex	Dec 20,Feb 2,3	Slight
	Irritable	Jan 10,11	Slight
	Stain, Red, Front Legs	Jan 10,11,16-26	Marked
	Stain, Brown, Front Legs	Jan 31-Feb 5	
		Feb 8-Mar 6	Moderate
	Alopecia, Front Leg	Feb 12	Slight
	Stain, Red, Nose	Feb 13	Slight
	Material, Red, Nose	Mar 10,11	Slight
86D00843	Alopecia, Front Legs	Jan 4-Mar 11	Marked
	Irritable	Feb 21,22,Mar 9	Slight
86D00849	Incr. Startle Reflex	Dec 16-18	
		Jan 12-15	Moderate
	Irritable	Jan 4,14,Feb 11	
		Mar 8	Moderate
	Stain, Red, Nose	Jan 21	Slight
	Stain, Dark, Nose	Feb 2	Slight
	Alopecia, Front Legs	Feb 9,11-Mar 12	Marked

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
FEMALE: 0 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00814	Irritable	Dec 26,Jan 6	Moderate
86D00815	Normal	N/A	N/A
86D00825	Normal	N/A	N/A
86D00832	Normal	N/A	N/A
86D00765	Incr. Startle Reflex	Dec 16-18,Jan 5	Moderate

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 1 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00752	Chewing Legs	Dec 16-22	Moderate
	Scab, R. Front Leg	Dec 22	Slight
	Alopecia, Front Legs	Dec 23-Jan 4	
		Jan 10-Mar 10	Marked
	Alopecia, Hind Legs	Jan 3,4	
		Jan 10-26	Slight
	Irritable	Dec 30-Jan 1	
		Jan 5,6,8-12,15	
		Feb 24-Mar 3	Moderate
	Stain, Red, Nose	Mar 9	Slight
86D00755	Incr. Startle Reflex	Jan 1,Feb 7	Slight
	Irritable	Feb 8,22-24	Moderate
86D00764	Alopecia, Front Legs	Jan 1-Mar 10	Marked
	Irritable	Jan 4,28	
		Feb 21,22	Slight
	Stain, Red, Nose, Mouth	Jan 15	Slight
	Stain, Brown, Nose	Feb 2	Slight
	Incr. Startle Reflex	Feb 17-24	Slight
86D00774	Material, Dark, Nose	Dec 28	Slight
	Incr. Startle Reflex	Jan 1-4,Feb 7-11	Slight
	Stain, Front Leg	Jan 3,4,11	Slight
	Alopecia, Front Leg	Jan 5-12,16-Mar 9	Marked
	Irritable	Jan 6-8, Feb 22	
		Feb 24-Mar 3	Slight
86D00795	Incr. Startle Reflex	Dec 16-18,Jan 1-4	Slight
	Irritable	Jan 5,6,8	Slight
	Material, Red, Nose	Mar 9	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 1 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00804	Alopecia, Front Legs	Jan 18-21,Feb 21	Slight
	Stain, Red, Nose	Jan 18,19	Slight
	Stain, Brown, Nose	Jan 29	Slight
	Material, Red, L. Eye	Mar 9,10	Slight
86D00838	Irritable	Dec 19-21,23-28	
		Jan 1,Feb 13-16	
		Feb 21,22,24-27	
		Mar 7	Slight
	Stain, Red, Back	Jan 4,18-20,31	Slight
	Stain, Red, Nose	Jan 13-15,22,23,31	
		Feb 3,7,9,11	
		Mar 7	Slight
	Rough Coat	Jan 8-21	Slight
	Material, Dark, Nose	Feb 12	Slight
	Alopecia, Front Leg	Feb 23,24	Slight
	Pinpoint Erosion, Eye	Mar 10	N/A
86D00840	Stain, Red, Neck	Dec 16	Slight
	Irritable	Dec 20,21,Jan 8,9	
		Feb 7,8,25	Moderate
	Incr. Startle Reflex	Jan 4	Slight
	Stain, Red, Head	Jan 3	Slight
	Stain, Red, Nose	Jan 15-17,20-24	Slight
	Stain, Red, Back	Jan 19	Slight
86D00850	Stain, Red, Nose	Jan 29	Slight
86D00855	Stain, Red, Nose	Dec 16,Jan 27	Slight
	Stain, Red, Ear	Dec 16,Jan 20	Slight
	Stain, Red, Front Legs	Jan 23,24,Mar 7,8	Slight
	Stain, Brown, Front Legs	Jan 31-Feb 5	Slight
	Material, Dark, Nose	Feb 12	Slight
	Irritable	Feb 22,23,25	Slight
	Material, Red, Ears	Mar 9,10	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28 DAY (INTERIM SACRIFICE)
FEMALE: 1 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00837	Irritable	Dec 28	Slight
86D00829	Emaciated	Dec 15	Slight
	Incr. Startle Reflex	Jan 1	Slight
86D00799	Chewing Front Legs	Dec 16-26	Slight
	Irritable	Dec 20,21,29,30	
		Jan 3-6	Slight
	Alopecia, Front Legs	Dec 27-31	Slight
	Stain, Red, Nose	Jan 4	Slight
86D00781	Irritable	Dec 20-22,30	
		Jan 4	Slight
	Incr. Startle Reflex	Jan 3	Slight
86D00758	Irritable	Dec 18-23,Jan 3,6	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 10 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00749	Rough Coat	Dec 16,17,19-21	
		Jan 8-13	Moderate
	Incr. Startle Reflex	Dec 16,17,23,Jan 1,2	Slight
	Dehydrated	Jan 1-3	Slight
	Chewing, Front Leg	Jan 1	Slight
	Stain, Red, Nose	Jan 4,Feb 21	Slight
	Stain, Red, Back	Jan 18,19	Moderate
	Scab, Right Side	Jan 30-Feb 1	Slight
	Irritable	Mar 7	Slight
86D00751	Incr. Startle Reflex	Dec 15-17,23	
		Jan 1-4,22	Slight
	Stain, Red, Nose	Dec 16,Jan 4,12,30	
		Mar 8	Slight
	Irritable	Dec 28,Jan 4,5,11,16	
		Mar 7-9	Moderate
	Material, Dark, Nose	Feb 9	Slight
	Aggressive	Feb 17	Moderate
86D00753	Stain, Red, Nose	Dec 16	Slight
	Incr. Startle Reflex	Jan 3,20-22	Slight
	Irritable	Jan 5, Feb 11,24	Moderate
	Rough Coat	Feb 8,9	Slight
86D00761	Incr. Startle Reflex	Dec 16,Feb 2,4,5	
		Feb 18-24	Slight
	Alopecia, Front Legs	Jan 19-22,30-Feb 2	
		Feb 4,5,12-23	Slight
	Stain, Red, Nose	Feb 1	Slight
	Material, Dark, Nose	Feb 5,21,22	Slight
	Irritable	Feb 7,8,12,23	Slight
86D00802	Incr. Startle Reflex	Dec 15-17	Slight
	Irritable	Dec 10,30-Jan 1	
		Feb 13-16	Slight
	Alopecia, Front Legs	Jan 19,20	Slight
	Stain, Red, Nose	Jan 20,21,29	Slight
	Material, Red, Nose	Feb 7,12	Slight
	Material, Dark, Nose	Mar 9	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 10 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00784	Incr. Startle Reflex	Dec 16	Slight
	Material, Red, Nose	Dec 27	Slight
	Irritable	Dec 28,29	Slight
	Alopecia, Front Legs	Jan 2-28	
		Jan 30-Mar 11	Moderate
	Alopecia, Hind Legs	Jan 10-22	Slight
	Alopecia, Perianal	Feb 1,2,4-20	Moderate
	Stain, Red, Nose	Jan 29,Feb 17-20	
		Mar 9-11	Moderate
	Stain, Red, Mouth	Feb 17,18	Moderate
86D00803	Incr. Startle Reflex	Dec 16	Slight
	Irritable	Jan 10,Mar 7,8	Moderate
86D00805	Incr. Startle Reflex	Dec 15-17,19-21	
		Jan 2,3,5-12,26-28	
		Feb 3,17,18	Moderate
	Irritable	Dec 16,Feb 7,23	
		Mar 7	Moderate
	Rough Coat	Dec 16,Jan 8-15	Slight
86D00826	Stain, Red, Nose	Dec 16	Slight
	Stain, Red, Back	Dec 16	Slight
	Incr. Startle Reflex	Dec 16,Jan 8	Slight
	Irritable	Dec 22,23,Jan 1,22	
		Feb 21,22	Marked
	Stain, Ears	Jan 2,3	Slight
	Aggressive	Feb 2,4,5,17	Moderate
	Material, Dark, Nose	Feb 12	Slight
86D00827	Stain, Red, Nose	Dec 16,Feb 2,6	Moderate
	Incr. Startle Reflex	Dec 16,23	
		Jan 4,22	Slight
	Irritable	Dec 22,23,Jan 2,3,6	
		Feb 12-17,22-24	
		Mar 8	Moderate
	Material. Dark, Nose	Dec 27	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
FEMALE: 10 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00846	Irritable	Dec 27,Jan 2,6	Slight
	Incr. Startle Reflex	Jan 2,3	Slight
86D00852	Normal	N/A	N/A
86D00789	Incr. Startle Reflex	Dec 16,17,19-24	
		Jan 1	Moderate
	Irritable	Dec 28-30	Moderate
	Alopecia, Front Legs	Jan 3,4	Marked
	Stain, Red, Front Leg	Jan 4	Slight
86D00771	Scab, Front Leg	Dec 13,14	Moderate
	Scab, Neck	Dec 15-18	Slight
	Irritable	Dec 23,24	Slight
	Scab, Back	Jan 1-4	Moderate
	Stain, Front Leg	Jan 1-4	Slight
	Alopecia, Back	Jan 7	
86D00759	Incr. Startle Reflex	Dec 16,17,Jan 1-4	Slight
	Alopecia, Front Legs	Jan 3,4	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00766	Incr. Startle Reflex	Dec 17,23-25	
		Jan 1,20,21	
		Feb 17-23	Slight
	Stain, Red, Nose	Jan 11,29	
		Feb 2,4,7	Slight
	Rough Coat	Jan 31,Feb 1	Slight
	Alopecia, Abdomen	Feb 2-18	Moderate
	Alopecia, Front Legs	Feb 17-Mar 9	Moderate
	Stain, Red, Ear	Feb 3	Slight
	Erosion, R. Eye	Mar 10	NA
86D00780	Irritable	Dec 15,16,23	
		Jan 3,7,Feb 7,8	
		Mar 7	Slight
	Incr. Startle Reflex	Jan 20,21	Slight
	Stain, Brown, Mouth	Jan 27	Slight
	Stain, Red, Nose	Feb 7	Slight
	Rough Coat	Mar 8	Marked
86D00787	Stain, Red, Nose	Dec 13	Slight
	Alopecia, Front Leg	Jan 30,31	Moderate
	Stain, Red, Neck	Feb 17,18	Slight
	Stain, Red, Ears	Jan 21,Feb 17,18	Slight
	Material, Red, Nose	Mar 10	Slight
	Conjunctivitis	Mar 10	Slight
86D00793	Irritable	Dec 17,Mar 8-10	Slight
	Hyperactive	Dec 29	
	Incr. Startle Reflex	Jan 1,26,Feb 2-4	Slight
	Alopecia, Front Legs	Jan 31-Feb 2,4	Slight
	Stain, Red, Nose	Mar 9	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00811	Material, Dark, Nose	Dec 26	Slight
	Scab, Front Leg	Jan 1	Slight
	Stain, Red, Front Legs	Jan 11,23	Slight
	Incr. Startle Reflex	Jan 20,21	Slight
	Stain, Red, Nose	Jan 23, Feb 21	
		Mar 7	Slight
	Rough Coat	Jan 27,28	
		Feb 8-11	Slight
	Stain, Brown, Front Leg	Jan 31-Feb 2	
		Feb 4,8-12	Slight
	Stain, Brown, Nose	Feb 23	Slight
	Stain, Red, Eye	Mar 8	Slight
	Lipid Inclusion, Cornea	Mar 10	
86D00812	Stain, Red, Back	Dec 16	Slight
	Incr. Startle Reflex	Jan 1-4	Slight
	Stain, Red, Nose	Jan 13	Slight
	Material, Red, Nose	Feb 24	Slight
	Irritable	Mar 7,8	Moderate
	Stain, Red, Eye	Mar 8	Slight
86D00844	Incr. Startle Reflex	Dec 16,17	
		Jan 1,3,4,12	
		Jan 20-23,26-28	
		Feb 3,17	Moderate
	Irritable	Jan 4,6,16	
		Mar 10	Slight
	Conjunctivitis	Mar 10	Slight
86D00848	Incr. Startle Reflex	Dec 22,Jan 20	Slight
	Irritable	Dec 23,24	
		Jan 5,10	Slight
	Rough Coat	Mar 7,8	Marked

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00851	Incr. Startle Reflex	Dec 16,17	
		Jan 4	Slight
	Irritable	Dec 19-22	
		Jan 5,15,26,27,30	
		Feb 5,7,24,Mar 7	Moderate
	Stain, Red, Nose	Jan 2,Feb 22	Slight
	Material, Dark, Nose	Feb 5	Slight
	Aggressive	Feb 8,13-18	
		Mar 9,10	Slight
86D00854	Incr. Startle Reflex	Dec 16,23,Jan 2-4	
		Jan 13,14,20	
		Feb 2	Slight
	Material. Dark, Eye	Dec 28-31	Moderate
	Stain, Red, Eyes	Jan 1-3,Mar 8	Moderate
	Stain, Red, Head	Jan 13	Slight
	Irritable	Jan 22-25,Mar 7	Moderate
	Material, Dark, Nose	Feb 9	Slight
	Material, Red, Ears	Feb 7	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
FEMALE: 30 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00842	Incr. Startle Reflex	Dec 16	Slight
	Irritable	Dec 17	Slight
86D00821	Incr. Startle Reflex	Dec 15,16,19-22	
		Jan 2,4	Slight
86D00794	Incr. Startle Reflex	Dec 15-17,Jan 1,3,4	Moderate
	Irritable	Dec 11,19-21,23-28	
		Jan 6	Slight
86D00790	Scab, Back	Dec 17-23	Slight
	Incr. Startle Reflex	Jan 1-4	Moderate
86D00785	Incr. Startle Reflex	Dec 17,23,Jan 4	Slight
	Irritable	Jan 3	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00760	Rough Coat	Dec 14	Slight
	Incr. Startle Reflex	Dec 25,Jan 1-3	
		Jan 10-12,16	
		Feb 3	Slight
	Material, Red, Nose	Dec 26	Slight
	Stain, Red, Nose	Jan 16,23-25	
		Feb 2,7,Mar 7	Marked
	Stain, Red, Ear	Feb 3,4	Slight
86D00762	Irritable	Dec 15	
		Jan 5,27,30	Slight
	Incr. Startle Reflex	Dec 16,17	
		Jan 1,14-16	Moderate
	Aggressive	Jan 16	Slight
86D00769	Incr. Startle Reflex	Dec 22,23	
		Jan 1-3,16,20-22	
		Feb 3,10,11	
		Mar 9	Slight
	Material, Dark, Nose	Jan 22	Slight
	Material, Red, Nose	Dec 27,Feb 5,12,13	
		Feb 22,Mar 10,11	Slight
	Irritable	Jan 4,5,Feb 12	
		Mar 8	Slight
	Stain, Red, Nose	Jan 12,15,16,20,27	
		Feb 8,9	Moderate
	Stain, Front Legs	Jan 16	Slight
	Aggressive	Feb 21	Slight
	Stain, Red, Eye	Mar 7	Slight
86D00770	Incr. Startle Reflex	Dec 16,Jan 1-4	
		Jan 7,8,Feb 7-9	Slight
	Irritable	Jan 2-4,11	Slight
	Stain, Red, Nose	Jan 2,Feb 2,12,21	Slight
	Stain, Dark, Nose	Feb 23	Slight
	Material, Red, Nose	Feb 7	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00819	Incr. Startle Reflex	Dec 15-24	
		Jan 7-10,13,21-23	
		Jan 27,28	
		Feb 7-14	Marked
	Irritable	Dec 25,Jan 4	
		Feb 8,10-12,21	
		Mar 10	Moderate
	Stain, Red, Nose	Jan 13,22	Slight
	Stain, Brown, Nose	Feb 13-17	
	Material, Red, Nose	Feb 7	Slight
	Material, Dark, Nose	Feb 21,22	Slight
86D00820	Incr. Startle Reflex	Dec 23,24,Jan 2-7	
		Feb 3-5	Slight
	Irritable	Jan 3	Slight
	Stain, Red, Eye	Jan 3,4	Slight
86D00831	Incr. Startle Reflex	Dec 16-21,Jan 2,3	
		Jan 12,20,21,26,27	
		Feb 7-10	Slight
	Irritable	Dec 12,19,23-28	
		Jan 9-12	
		Feb 11,12	Slight
	Stain, Red, Nose	Jan 23,Feb 18-20	Slight
	Aggressive	Feb 17	Slight
86D00845	Incr. Startle Reflex	Dec 16,17,29	
		Jan 20,21	Slight
	Irritable	Dec 19-26,Jan 2,3	
		Feb 1,2,7-9,21,24	Moderate
	Stain, Red, Nose	Jan 13	Slight
	Stain, Red, Eye	Feb 17-25	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00847	Material, Red, Nose	Dec 10	Slight
	Incr. Startle Reflex	Dec 15-17,20-25	
		Jan 2-6,10,15,16	
		Jan 26,Feb 9,25	Moderate
	Material, Dark, Nose	Dec 25,Jan 8	Slight
	Stain, Red, Head	Jan 1-4	Slight
	Stain, Red, Nose	Jan 4,10,12,13,15	
		Jan 16,21-24,Feb 1-4	
		Feb 21,23,24	
		Mar 9-12	Slight
	Irritable	Jan 13,30,Feb 7-11	
		Feb 22-24	Moderate
	Aggressive	Feb 5	Moderate
	Stain, Brown, Nose	Feb 10-13	Slight
	Stain, Brown, Eye	Feb 11	Slight
	Stain, Red, Eye	Feb 21,22	Slight
	Alopecia, Front Legs	Feb 12-16	Moderate
	Alopecia, Flank	Feb 13-16	Slight
86D00856	Incr. Startle Reflex	Dec 17,Jan 15,20	
		Feb 3-5	Slight
	Stain, Clear, Leg	Jan 3	Moderate
	Stain, Red, Nose	Feb 2	Slight
	Stain, Brown, Legs	Feb 12-20	Slight
	Irritable	Feb 13-17,22,24	Moderate
	Alopecia,Front Leg	Feb 21-Mar 4	Slight
	Material, Dark, Nose	Feb 21	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
FEMALE: 60 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00841	Irritable	Dec 19,Jan 1	Slight
	Incr. Startle Reflex	Jan 1	Slight
86D00835	Irritable	Dec 18,23,28	Slight
86D00797	Incr. Startle Reflex	Dec 16-18	Slight
	Hypertonia	Dec 16	Slight
	Material, Dark, Nose	Dec 26,28	Slight
	Irritable	Dec 26	Slight
86D00782	Incr. Startle Reflex	Dec 14,15,23	
		Jan 1	Moderate
	Irritable	Dec 28	Slight
	Stain, Red, Front Leg	Jan 4	Slight
86D00775	Incr. Startle Reflex	Dec 16,23,Jan 1-3	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00750	Incr. Startle Reflex	Dec 13,16,18,19	
		Jan 13-15,Feb 2	
		Feb 17,18	Marked
	Stain, Red, Nose	Jan 13,20,26,27	Slight
	Material, Dark, Nose	Jan 22	Slight
	Stain, Dark, Nose	Jan 23	Slight
	Material, Red, Nose	Feb 5	Slight
	Stain, Brown, Nose	Feb 9,12	Moderate
	Alopecia, Front Leg	Feb 17,18	Slight
	Conjunctivitis	Feb 7,8	Slight
86D00783	Incr. Startle Reflex	Dec 16,17,29,Jan 10	
		Jan 26-28	Slight
	Stain, Red, Nose	Jan 15,Feb 5-7	Slight
	Irritable	Jan 30	Slight
86D00792	Dehydrated	Dec 16-24	Slight
	Hypertonia	Dec 17-19	Moderate
	Incr. Startle Reflex	Dec 17,18,Jan 1,2	
		Feb 3-5	Slight
	Irritable	Dec 24-26,Jan 1,10	
		Jan 30	Slight
	Hyperactive	Feb 5	
	Aggressive	Mar 8,9	Slight
86D00798	Incr. Startle Reflex	Dec 19-22,Jan 1	
		Feb 7-9	Slight
	Irritable	Dec 11,Jan 1	Slight
	Incr. Salivation	Jan 2	Slight
	Alopecia, Front Legs	Jan 4-Mar 10	Marked
	Alopecia, Hind Legs	Jan 4-26	Moderate
	Alopecia, Tail	Jan 17-22	Moderate
86D00809	Incr. Startle Reflex	Dec 16,17,Jan 1	Slight
	Irritable	Jan 1,3-5,Feb 7-10	Marked
	Stain, Brown, Nose	Feb 12	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00813	Rough Coat	Dec 16,Jan 16	Slight
	Incr. Startle Reflex	Dec 16,17,Jan 13	Slight
	Material, Dark, Nose	Dec 25,Jan 22	Slight
	Irritable	Jan 1,7,30,Feb 7,24	Marked
	Stain, Red, Nose	Jan 13	Slight
	Stain, Dark, Nose	Jan 23	Slight
	Stain, Brown, Front Legs	Jan 31-Feb 4	Slight
	Stain, Red, Eye	Feb 6-8,12-16	Moderate
	Conjunctivitis	Feb 8-16	Marked
	Alopecia, Front Legs	Feb 12	Slight
	Alopecia, Hind Legs	Feb 12	Slight
86D00816	Incr. Startle Reflex	Dec 16-18,24,25	
		Jan 29-31,Feb 3	Slight
	Stain, Red, Neck	Dec 16,17	Slight
	Stain, Red, Front Legs	Jan 1-4,16,17	
		Mar 7,8	Moderate
	Stain, Red, Nose	Jan 11,12	Slight
	Irritable	Jan 16,Feb 10	Slight
	Alopecia, Front Legs	Jan 19	Slight
	Stain, Brown, Front Legs	Jan 31-Feb 4	
		Feb 11-22	Moderate
86D00817	Stain, Red, Back	Dec 16	Slight
	Incr. Startle Reflex	Dec 17,18,Jan 2,3	
		Jan 26,27	Slight
	Stain, Red, Ears	Jan 13-16,20-22	
		Feb 1-18,Mar 8-11	Moderate
	Irritable	Jan 23-26,Feb 22-24	Slight
	Conjunctivitis	Feb 6,7	Slight
	Stain, Red, Nose	Feb 12	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00822	Irritable	Dec 17-19,Jan 23-25	
		Jan 30,Feb 10,21,22	Slight
	Incr. Startle Reflex	Dec 17,18,20,21	
		Jan 4	Slight
	Aggressive	Jan 26,27,Feb 23,24	
		Mar 7-10	Moderate
	Stain, Red, Nose	Jan 29	Slight
	Stain, Red, Mouth	Jan 29	Slight
	Stain, Red, Ears	Feb 7	Slight
	Conjunctivitis	Feb 7	Slight
86D00830	Incr. Startle Reflex	Dec 16-18,31	
		Jan 1,8,12-16,29-31	
		Feb 12,13,17,24	Slight
	Irritable	Dec 17,24-27	
		Jan 1,4-9,21-28	
		Feb 12,18-20,24	Slight
	Material, Red, Nose	Dec 26	Slight
	Material, Dark, Nose	Jan 8	Slight
	Stain, Red, Ears	Jan 21-Feb 3	Slight
	Diarrhea	Jan 26	Slight

Appendix L (cont.): INDIVIDUAL ANIMAL HISTORIES

28-DAY INTERIM SACRIFICE
FEMALE: 90 mg/kg/day PYRIDOSTIGMINE BROMIDE (cont.)

Animal Number	Clinical Signs	Dates Observed (1986/87)	Severity
86D00839	Incr. Startle Reflex	Dec 15,17-23	
		Jan 1-4	Moderate
	Hypertonia	Dec 17,18	Slight
	Irritable	Dec 17,18,28,Jan 1	Slight
	Stain, Clear, Abdomen	Jan 1	Moderate
	Alopecia, Front Leg	Jan 3,4	Slight
86D00779	Scab, Back	Dec 16-Jan 4	Moderate
	Incr. Startle Reflex	Dec 20-22	Slight
86D00773	Stain, Red, Ear	Dec 16	Slight
	Incr. Startle Reflex	Dec 17,18,Jan 1,2	Slight
	Irritable	Dec 19-21,Jan 1,4	Slight
	Aggressive	Dec 28,29	Slight
86D00757	Hypertonia	Dec 16	Slight
	Stain, Red, Neck	Dec 16	Slight
	Incr. Startle Reflex	Dec 17-25,31,Jan 1	Moderate
	Irritable	Dec 31	Slight
	Stain, Red, Ear	Jan 2	Slight
	Stain, Red, Eyes	Jan 4	Slight
86D00754	Incr. Startle Reflex	Dec 17,19	Slight

Appendix M: SERUM CHEMISTRY

List of Serum Chemistry Abbreviations/Units

ACHE	Erythrocyte Acetylcholinesterase (U/ml)
CHE	Plasma Cholinesterase (U/ml)
ALT	Alanine Aminotransferase (U/l)
AST	Aspartate Aminotransferase (U/l)
ALK	Alkaline Phosphatase (U/l)
LDH	Lactate Dehydrogenase (U/l)
CK	Creatine Phosphokinase (U/l)
BILI	Total Bilirubin (mg/dl)
CHOL	Cholesterol (mg/dl)
TRIG	Triglyceride (mg/dl)
URIC	Uric Acid (mg/dl)
TP	Total Protein (g/dl)
ALB	Albumin (g/dl)
GLU	Glucose (mg/dl)
BUN	Blood Urea Nitrogen (mg/dl)
CR	Creatinine (mg/dl)
CAL	Calcium (mg/dl)
PHOS	Phosphorus (mg/dl)
NA	Sodium (Meq/l)
CL	Chloride (Meq/l)
K	Potassium (Meq/l)
IRON	Iron (µg/dl)
MAG	Magnesium (mg/dl)
NT	Not Taken

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00512	M	baseline	0	1.662	0.251	58.7	195.1	196.8	954.7	1606.0	0.00
86D00519	M	baseline	0	1.496	0.259	48.5	157.7	220.8	999.1	1275.1	0.00
86D00529	M	baseline	0	1.778	0.438	76.6	99.5	355.9	434.3	621.7	0.00
86D00564	M	baseline	0	1.129	0.365	50.0	141.1	185.0	799.2	917.8	0.00
86D00637	M	baseline	0	1.313	0.291	50.9	111.3	287.0	667.2	889.4	0.00
86D00673	M	baseline	0	1.411	0.446	55.8	110.2	227.5	279.8	593.2	0.00
86D00687	M	baseline	0	1.314	0.422	66.8	278.1	246.0	763.8	866.8	0.00
86D00702	M	baseline	0	1.470	0.275	47.5	80.0	314.2	376.9	496.4	0.00
86D00711	M	baseline	0	NT	NT	NT	NT	NT	NT	NT	NT
86D00714	M	baseline	0	1.327	0.283	54.4	75.0	258.7	141.2	412.1	0.00
Mean				1.4333	0.3367	56.58	138.67	254.66	601.80	853.17	0.000
Std Dev				0.1967	0.0810	9.61	64.79	55.92	305.44	386.24	0.000
86D00756	F	baseline	0	1.641	0.699	38.8	178.7	179.0	717.5	2202.9	0.00
86D00767	F	baseline	0	1.604	0.556	38.5	126.3	208.6	387.7	755.0	0.00
86D00777	F	baseline	0	2.603	0.592	40.3	172.3	223.8	613.9	1775.6	0.00
86D00786	F	baseline	0	2.536	0.556	46.7	105.2	236.9	407.4	619.4	0.00
86D00791	F	baseline	0	1.044	0.628	42.4	117.0	184.4	576.4	1073.9	0.00
86D00800	F	baseline	0	0.860	0.486	41.7	174.6	223.2	963.8	2805.3	0.00
86D00807	F	baseline	0	1.559	0.601	41.6	129.5	200.7	494.9	711.2	0.00
86D00808	F	baseline	0	1.128	0.556	35.2	100.0	156.4	390.1	634.5	0.00
86D00823	F	baseline	0	0.973	0.529	52.8	358.8	221.7	620.1	8468.0	0.00
86D00828	F	baseline	0	1.772	0.796	59.5	243.0	249.5	1682.9	10067.1	0.00
Mean				1.5720	0.5999	43.75	170.54	208.42	685.47	2911.29	0.000
Std Dev				0.6128	0.0900	7.35	79.25	28.55	392.17	3451.05	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00512	M	baseline	0	65.8	167.0	2.8	5.4	2.32	196.2	19.0	0.37
86D00519	M	baseline	0	43.3	74.1	2.2	5.2	2.89	246.0	16.8	0.37
86D00529	M	baseline	0	77.4	86.0	3.2	5.4	3.02	241.6	15.2	0.56
86D00564	M	baseline	0	55.9	117.8	2.3	5.1	2.74	248.4	11.7	0.40
86D00637	M	baseline	0	69.9	71.2	1.4	5.3	2.90	254.9	14.2	0.42
86D00673	M	baseline	0	55.9	71.5	2.7	4.8	2.74	186.4	13.5	0.42
86D00687	M	baseline	0	46.1	107.1	2.6	4.7	2.62	241.3	16.6	0.42
86D00702	M	baseline	0	55.4	62.2	2.3	5.2	2.83	284.9	16.0	0.55
86D00711	M	baseline	0	NT	NT	NT	NT	NT	NT	NT	NT
86D00714	M	baseline	0	54.6	71.0	2.5	5.2	2.92	240.8	19.6	0.55
Mean				58.26	91.99	2.44	5.14	2.776	237.83	15.84	0.451
Std Dev				10.97	33.65	0.50	0.25	0.208	29.79	2.53	0.079
86D00756	F	baseline	0	49.4	56.6	3.1	5.4	3.25	258.6	23.2	0.35
86D00767	F	baseline	0	62.9	94.1	1.9	5.1	2.86	254.1	19.2	0.51
86D00777	F	baseline	0	62.7	143.4	2.4	4.7	2.75	246.2	16.5	0.36
86D00786	F	baseline	0	59.7	67.1	2.7	5.5	3.19	261.9	17.7	0.59
86D00791	F	baseline	0	59.4	76.9	2.2	5.3	3.34	286.5	17.1	0.51
86D00800	F	baseline	0	71.9	50.7	2.2	4.9	2.69	278.1	16.2	0.33
86D00807	F	baseline	0	69.8	82.7	4.0	5.7	3.30	242.0	14.4	0.48
86D00808	F	baseline	0	62.5	40.1	2.7	5.3	3.06	317.3	12.6	0.66
86D00823	F	baseline	0	62.3	76.1	2.9	5.0	2.69	275.0	14.8	0.39
86D00828	F	baseline	0	47.0	69.6	3.9	4.8	2.70	222.2	13.3	0.15
Mean				60.76	75.73	2.80	5.17	2.983	264.19	16.50	0.433
Std Dev				7.75	28.56	0.70	0.32	0.273	26.55	3.11	0.147

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00512	M	baseline	0	11.2	9.90	146	103	6.1	341	2.75
86D00519	M	baseline	0	10.9	9.20	148	100	6.3	337	2.87
86D00529	M	baseline	0	12.0	11.30	147	101	6.7	343	2.94
86D00564	M	baseline	0	10.6	9.40	151	101	6.0	276	2.57
86D00637	M	baseline	0	11.4	9.10	147	103	6.3	174	2.75
86D00673	M	baseline	0	11.2	9.40	148	104	6.7	356	2.78
86D00687	M	baseline	0	10.0	9.00	145	105	6.7	454	2.59
86D00702	M	baseline	0	10.8	10.00	145	98	6.3	170	2.68
86D00711	M	baseline	0	NT	NT	NT	NT	NT	NT	NT
86D00714	M	baseline	0	10.7	11.20	140	101	7.4	135	2.58
Mean				10.98	9.833	146.3	101.8	6.50	287.3	2.723
Std Dev				0.56	0.870	3.0	2.2	0.43	106.6	0.131
86D00756	F	baseline	0	11.1	9.60	152	104	6.9	251	2.79
86D00767	F	baseline	0	11.0	8.00	149	105	6.1	310	2.43
86D00777	F	baseline	0	10.7	7.50	147	105	5.9	372	2.58
86D00786	F	baseline	0	11.5	9.20	147	103	7.9	246	2.92
86D00791	F	baseline	0	11.6	10.10	147	102	6.1	267	2.87
86D00800	F	baseline	0	11.2	10.50	150	104	5.6	359	2.66
86D00807	F	baseline	0	12.3	9.80	156	102	6.7	310	3.03
86D00808	F	baseline	0	11.2	10.70	152	103	6.8	392	3.04
86D00823	F	baseline	0	11.0	11.40	147	104	7.6	168	2.65
86D00828	F	baseline	0	10.4	11.60	149	103	8.2	321	2.79
Mean				11.20	9.840	149.6	103.5	6.78	299.6	2.776
Std Dev				0.52	1.338	3.0	1.1	0.89	68.0	0.198

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00543	M	0 mg/kg	28	2.228	0.321	78.3	247.8	179.7	1127.4	3697.4	0.00
86D00620	M	0 mg/kg	28	3.070	0.288	54.4	131.5	234.9	482.2	1561.7	0.00
86D00680	M	0 mg/kg	28	2.470	0.288	36.1	87.6	143.8	328.2	972.9	0.00
86D00681	M	0 mg/kg	28	2.048	0.279	41.8	102.9	278.6	364.9	631.6	0.00
86D00712	M	0 mg/kg	28	0.604	0.262	42.1	75.9	143.9	298.6	425.4	0.00
Mean				2.0840	0.2876	50.54	129.14	196.18	520.26	1457.80	0.000
Std Dev				0.9129	0.0215	16.89	69.52	59.25	346.49	1323.84	0.000
86D00506	M	1.0 mg/kg	28	0.886	0.337	66.4	114.3	211.8	676.0	826.0	0.00
86D00507	M	1.0 mg/kg	28	1.230	0.328	43.4	105.2	217.3	366.7	704.3	0.00
86D00548	M	1.0 mg/kg	28	1.837	0.361	47.0	71.1	255.3	187.6	370.4	0.00
86D00606	M	1.0 mg/kg	28	1.779	0.205	46.0	108.7	146.1	600.4	1316.0	0.00
86D00733	M	1.0 mg/kg	28	1.992	0.262	45.9	74.7	162.1	465.0	295.5	0.00
Mean				1.5448	0.2986	49.74	94.80	198.52	459.14	702.44	0.000
Std Dev				0.4673	0.0639	9.41	20.29	44.24	193.19	408.53	0.000
86D00510	M	10.0 mg/kg	28	1.482	0.131	45.3	97.7	294.1	262.9	735.0	0.00
86D00520	M	10.0 mg/kg	28	1.987	0.180	98.2	257.2	215.0	2732.3	784.5	0.00
86D00599	M	10.0 mg/kg	28	1.863	0.131	42.1	99.2	222.7	715.5	635.9	0.00
86D00602	M	10.0 mg/kg	28	1.131	0.123	47.5	90.5	168.6	690.3	537.5	0.00
86D00713	M	10.0 mg/kg	28	0.746	0.205	40.9	101.6	264.4	235.7	690.9	0.00
Mean				1.4418	0.1540	54.80	129.24	232.96	927.34	676.76	0.000
Std Dev				0.5141	0.0364	24.40	71.65	48.21	1034.26	95.21	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00554	M	30.0 mg/kg	28	0.633	0.090	41.2	129.5	225.5	1443.8	1118.7	0.00
86D00593	M	30.0 mg/kg	28	1.411	0.115	50.3	111.6	141.0	971.4	1025.9	0.00
86D00604	M	30.0 mg/kg	28	1.095	0.082	35.6	104.7	216.1	482.3	559.3	0.00
86D00644	M	30.0 mg/kg	28	1.969	0.071	47.6	111.5	208.7	758.9	1103.0	0.00
86D00645	M	30.0 mg/kg	28	1.767	0.104	36.4	69.5	149.0	146.1	742.3	0.00
Mean				1.3750	0.0924	42.22	105.36	188.06	760.50	909.84	0.000
Std Dev				0.5331	0.0174	6.58	22.06	39.86	491.49	247.66	0.000
86D00509	M	60.0 mg/kg	28	0.000	0.112	50.1	102.2	244.5	526.3	797.0	0.00
86D00533	M	60.0 mg/kg	28	0.000	0.071	53.8	90.4	319.5	563.0	745.7	0.00
86D00621	M	60.0 mg/kg	28	0.345	0.062	38.3	84.5	180.8	390.7	443.7	0.00
86D00648	M	60.0 mg/kg	28	1.258	0.146	57.5	162.6	125.8	315.6	2081.9	0.00
86D00726	M	60.0 mg/kg	28	1.867	0.071	49.6	108.3	164.0	836.5	710.0	0.00
Mean				0.6940	0.0924	49.86	109.60	206.92	526.42	955.66	0.000
Std Dev				0.8335	0.0357	7.21	31.08	76.14	200.22	644.23	0.000
86D00523	M	90.0 mg/kg	28	1.279	0.096	41.0	95.3	227.3	340.9	674.7	0.00
86D00552	M	90.0 mg/kg	28	1.825	0.087	42.0	93.7	277.3	506.3	547.0	0.00
86D00587	M	90.0 mg/kg	28	1.762	0.079	42.5	84.6	181.6	406.9	483.6	0.00
86D00631	M	90.0 mg/kg	28	1.188	0.071	37.9	85.4	208.6	475.9	588.4	0.00
86D00674	M	90.0 mg/kg	28	1.359	0.071	37.6	80.8	168.7	638.1	513.0	0.00
Mean				1.4826	0.0808	40.20	87.96	212.70	473.62	561.34	0.000
Std Dev				0.2910	0.0108	2.30	6.24	42.74	112.02	74.45	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00543	M	0 mg/kg	28	66.0	198.3	2.2	4.7	2.19	202.5	20.6	0.47
86D00620	M	0 mg/kg	28	47.2	407.9	2.0	5.9	3.29	312.0	23.7	0.84
86D00680	M	0 mg/kg	28	39.7	139.2	2.1	6.0	2.88	261.7	17.2	0.60
86D00681	M	0 mg/kg	28	82.6	102.0	6.7	6.7	3.10	396.0	16.7	0.64
36D00712	M	0 mg/kg	28	84.6	65.0	3.3	6.0	3.00	254.9	18.6	0.71
Mean				64.02	182.48	3.26	5.86	2.892	285.42	19.36	0.652
Std Dev				20.29	135.29	1.99	0.72	0.420	72.98	2.86	0.137
86D00506	M	1.0 mg/kg	28	84.0	80.5	2.7	5.5	2.63	307.5	20.0	0.65
86D00507	M	1.0 mg/kg	28	76.8	111.9	3.6	5.7	3.21	294.6	17.6	0.61
86D00548	M	1.0 mg/kg	28	43.0	86.6	2.8	6.2	2.94	314.2	21.3	0.72
86D00606	M	1.0 mg/kg	28	74.5	120.0	1.6	5.4	2.63	237.0	24.3	0.51
86D00733	M	1.0 mg/kg	28	75.3	199.1	1.3	5.3	2.65	233.9	17.8	0.62
Mean				70.72	119.62	2.40	5.62	2.812	277.44	20.20	0.622
Std Dev				15.95	47.43	0.94	0.36	0.258	38.99	2.76	0.076
86D00510	M	10.0 mg/kg	28	76.7	227.6	5.3	6.2	3.31	329.0	21.7	0.76
86D00520	M	10.0 mg/kg	28	28.1	166.6	0.7	5.2	2.45	210.3	19.6	0.27
86D00599	M	10.0 mg/kg	28	71.7	126.8	3.3	5.8	3.09	245.3	18.0	0.58
86D00602	M	10.0 mg/kg	28	70.4	94.1	1.9	5.7	2.82	247.9	18.9	0.63
86D00713	M	10.0 mg/kg	28	93.3	92.6	3.5	5.5	2.98	320.3	20.4	0.80
Mean				68.04	141.54	2.94	5.68	2.930	270.56	19.72	0.608
Std Dev				24.12	56.78	1.74	0.37	0.322	51.65	1.42	0.209

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00554	M	30.0 mg/kg	28	75.9	75.8	1.1	5.5	2.87	273.7	20.5	0.71
86D00593	M	30.0 mg/kg	28	77.1	102.8	1.6	5.4	2.95	239.5	22.9	0.76
86D00604	M	30.0 mg/kg	28	80.3	173.0	1.1	6.2	3.03	270.2	16.8	0.58
86D00644	M	30.0 mg/kg	28	69.6	157.8	1.3	5.6	2.85	231.4	18.0	0.64
86D00645	M	30.0 mg/kg	28	47.7	106.7	2.1	5.2	2.77	247.3	15.0	0.71
Mean				70.12	123.22	1.44	5.58	2.894	252.42	18.64	0.680
Std Dev				13.12	40.66	0.42	0.38	0.099	18.73	3.11	0.070
86D00509	M	60.0 mg/kg	28	50.5	88.4	2.8	6.1	3.41	233.4	18.3	0.68
86D00533	M	60.0 mg/kg	28	38.5	142.3	2.0	6.6	3.00	184.8	21.7	0.62
86D00621	M	60.0 mg/kg	28	75.2	NT	1.2	5.4	2.86	249.6	20.6	0.63
86D00648	M	60.0 mg/kg	28	58.2	164.2	4.2	5.5	2.80	347.9	14.8	0.69
86D00726	M	60.0 mg/kg	28	54.4	95.7	1.8	5.8	2.91	222.4	19.8	0.78
Mean				55.36	122.65	2.40	5.88	2.996	247.62	19.04	0.680
Std Dev				13.33	36.57	1.16	0.49	0.243	60.92	2.67	0.064
86D00523	M	90.0 mg/kg	28	49.7	93.1	4.8	6.0	3.13	243.6	16.6	0.71
86D00552	M	90.0 mg/kg	28	53.0	75.1	2.4	5.3	2.95	242.1	17.0	0.59
86D00587	M	90.0 mg/kg	28	54.1	126.8	3.5	5.7	2.98	278.9	12.2	0.64
86D00631	M	90.0 mg/kg	28	29.9	98.9	3.8	5.6	2.88	256.5	19.2	0.50
86D00674	M	90.0 mg/kg	28	45.8	77.6	2.3	5.2	2.80	224.8	15.2	0.60
Mean				46.50	94.30	3.36	5.56	2.948	249.18	16.04	0.608
Std Dev				9.83	20.77	1.04	0.32	0.123	20.08	2.58	0.077

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00543	M	0 mg/kg	28	10.1	9.50	143	97	8.1	240	2.58
86D00620	M	0 mg/kg	28	11.0	11.90	145	98	5.1	126	2.75
86D00680	M	0 mg/kg	28	10.7	9.70	143	99	5.5	217	2.89
86D00681	M	0 mg/kg	28	13.6	8.10	142	102	6.9	171	3.60
86D00712	M	0 mg/kg	28	11.8	8.70	139	101	7.0	203	2.96
Mean				11.44	9.580	142.4	99.4	6.52	191.4	2.956
Std Dev				1.35	1.446	2.2	2.1	1.22	44.3	0.388
86D00506	M	1.0 mg/kg	28	10.4	9.80	147	101	5.4	299	2.65
86D00507	M	1.0 mg/kg	28	10.8	8.40	146	104	8.5	179	3.01
86D00548	M	1.0 mg/kg	28	10.8	9.10	146	101	7.7	215	2.66
86D00606	M	1.0 mg/kg	28	11.4	10.40	142	112	6.0	209	2.50
86D00733	M	1.0 mg/kg	28	11.3	8.00	142	104	5.2	194	2.07
Mean				10.94	9.140	144.6	104.4	6.56	219.2	2.578
Std Dev				0.41	0.984	2.4	4.5	1.46	46.7	0.340
86D00510	M	10.0 mg/kg	28	11.2	11.00	149	100	9.9	106	3.25
86D00520	M	10.0 mg/kg	28	9.7	8.20	147	103	6.7	215	2.22
86D00599	M	10.0 mg/kg	28	10.8	9.30	142	102	7.6	190	3.00
86D00602	M	10.0 mg/kg	28	10.4	10.10	147	101	7.8	143	2.47
86D00713	M	10.0 mg/kg	28	12.2	9.90	142	104	7.0	172	2.85
Mean				10.86	9.700	145.4	102.0	7.80	165.2	2.758
Std Dev				0.93	1.037	3.2	1.6	1.25	42.2	0.413

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00554	M	30.0 mg/kg	28	9.6	8.50	147	103	5.4	161	2.27
86D00593	M	30.0 mg/kg	28	9.8	8.60	147	101	6.1	137	2.65
86D00604	M	30.0 mg/kg	28	11.6	8.10	142	100	6.1	245	2.56
86D00644	M	30.0 mg/kg	28	10.5	9.60	145	102	6.5	178	2.53
86D00645	M	30.0 mg/kg	28	10.8	7.30	140	101	4.6	166	2.22
Mean				10.46	8.420	144.2	101.4	5.74	177.4	2.446
Std Dev				0.80	0.835	3.1	1.1	0.75	40.6	0.190
86D00509	M	60.0 mg/kg	28	11.4	10.30	143	105	6.1	195	2.94
86D00533	M	60.0 mg/kg	28	10.6	8.60	148	99	5.8	153	2.42
86D00621	M	60.0 mg/kg	28	10.0	9.30	152	99	7.5	187	2.25
86D00648	M	60.0 mg/kg	28	10.4	10.50	148	104	7.6	113	2.97
86D00726	M	60.0 mg/kg	28	11.0	9.80	146	102	6.1	170	2.54
Mean				10.68	9.700	147.4	101.8	6.62	163.6	2.624
Std Dev				0.54	0.771	3.3	2.8	0.86	32.6	0.319
86D00523	M	90.0 mg/kg	28	12.0	9.80	143	100	8.6	234	3.04
86D00552	M	90.0 mg/kg	28	10.5	9.50	141	104	6.4	133	2.82
86D00587	M	90.0 mg/kg	28	11.1	10.10	146	101	8.3	143	2.95
86D00631	M	90.0 mg/kg	28	11.3	8.80	141	101	5.7	184	2.82
86D00674	M	90.0 mg/kg	28	10.7	9.80	138	100	6.6	204	2.64
Mean				11.12	9.600	141.8	101.2	7.12	179.6	2.854
Std Dev				0.58	0.495	2.9	1.6	1.26	42.1	0.152

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00765	F	0 mg/kg	28	1.638	0.398	35.5	130.2	227.0	537.6	769.5	0.00
86D00814	F	0 mg/kg	28	1.376	0.398	35.5	97.6	125.8	248.6	524.6	0.00
86D00815	F	0 mg/kg	28	1.463	0.581	36.9	83.6	184.5	323.9	339.8	0.00
86D00825	F	0 mg/kg	28	1.513	0.416	33.2	83.6	149.3	198.7	177.3	0.00
86D00832	F	0 mg/kg	28	1.387	0.468	42.4	95.7	138.9	342.4	526.1	0.00
Mean				1.4754	0.4522	36.70	98.14	165.10	330.24	467.46	0.000
Std Dev				0.1069	0.0775	3.45	19.08	40.89	129.57	222.72	0.000
86D00758	F	1.0 mg/kg	28	1.399	1.082	64.2	228.7	146.4	1361.2	7757.0	0.00
86D00781	F	1.0 mg/kg	28	1.776	0.754	40.0	125.8	98.0	912.2	624.0	0.00
86D00799	F	1.0 mg/kg	28	1.789	1.091	36.4	104.8	150.3	726.0	760.5	0.00
86D00829	F	1.0 mg/kg	28	1.326	0.433	44.1	122.9	254.6	547.8	581.5	0.00
86D00837	F	1.0 mg/kg	28	1.667	0.728	56.4	375.0	152.1	1213.6	2376.9	0.00
Mean				1.5914	0.8176	48.22	191.44	160.28	952.16	2419.98	0.000
Std Dev				0.2158	0.2760	11.69	113.57	57.30	336.12	3075.92	0.000
86D00759	F	10.0 mg/kg	28	1.504	0.598	40.9	93.5	74.1	635.8	519.9	0.00
86D00771	F	10.0 mg/kg	28	1.003	0.563	42.5	117.3	148.7	523.3	576.0	0.00
86D00789	F	10.0 mg/kg	28	1.219	0.389	34.3	86.6	122.3	430.5	489.4	0.00
86D00846	F	10.0 mg/kg	28	1.219	0.650	52.1	183.0	99.0	626.6	1044.1	0.00
86D00852	F	10.0 mg/kg	28	1.068	0.433	45.0	146.4	152.7	544.2	800.1	0.00
Mean				1.2026	0.5266	42.96	125.36	119.36	552.08	685.90	0.000
Std Dev				0.1932	0.1111	6.46	39.84	33.33	84.02	234.30	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00785	F	30.0 mg/kg	28	1.113	0.424	40.6	83.0	277.7	290.6	331.4	0.00
86D00790	F	30.0 mg/kg	28	1.050	0.687	52.3	121.2	122.3	443.7	619.8	0.00
86D00794	F	30.0 mg/kg	28	0.933	0.329	31.0	86.2	145.0	250.8	362.0	0.00
86D00821	F	30.0 mg/kg	28	0.734	0.233	45.6	285.7	112.5	986.6	450.3	0.00
86D00842	F	30.0 mg/kg	28	0.718	0.477	35.7	99.4	171.9	194.5	509.2	0.00
Mean				0.9096	0.4300	41.04	135.10	165.88	433.24	454.54	0.000
Std Dev				0.1797	0.1712	8.32	85.52	66.57	322.86	116.24	0.000
86D00775	F	60.0 mg/kg	28	0.614	0.468	33.3	127.8	110.2	768.3	916.3	0.00
86D00782	F	60.0 mg/kg	28	0.917	0.294	37.6	90.0	88.4	360.7	421.3	0.00
86D00797	F	60.0 mg/kg	28	0.742	0.329	31.9	58.1	89.5	199.0	230.7	0.00
86D00835	F	60.0 mg/kg	28	0.640	0.233	33.8	95.8	170.3	752.6	635.7	0.00
86D00841	F	60.0 mg/kg	28	0.827	0.156	40.3	210.2	118.0	894.6	1173.3	0.00
Mean				0.7480	0.2960	35.38	116.38	115.28	595.04	675.46	0.000
Std Dev				0.1269	0.1165	3.47	57.98	33.34	298.47	377.44	0.000
86D00754	F	90.0 mg/kg	28	0.550	0.130	39.9	96.1	151.8	514.8	492.8	0.00
86D00757	F	90.0 mg/kg	28	0.632	0.363	32.6	100.5	151.2	648.8	544.1	0.00
86D00773	F	90.0 mg/kg	28	0.609	0.311	36.1	97.7	95.2	672.0	468.6	0.00
86D00779	F	90.0 mg/kg	28	0.747	0.303	41.8	130.7	194.0	1008.9	756.9	0.00
86D00839	F	90.0 mg/kg	28	0.369	0.320	48.4	225.4	195.8	549.2	1354.4	0.00
Mean				0.5814	0.2854	39.76	130.08	157.60	678.74	723.36	0.000
Std Dev				0.1386	0.0899	5.99	55.15	41.09	195.96	370.65	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00765	F	0 mg/kg	28	78.5	41.7	1.5	5.9	2.94	239.8	19.0	0.62
86D00814	F	0 mg/kg	28	74.5	79.9	1.6	5.8	3.73	240.3	17.0	0.60
86D00815	F	0 mg/kg	28	71.9	55.5	2.2	5.9	3.30	205.3	16.9	0.60
86D00825	F	0 mg/kg	28	44.4	64.7	1.4	5.2	2.72	191.1	18.9	0.46
86D00832	F	0 mg/kg	28	61.5	61.8	1.7	5.5	2.93	243.3	17.0	0.59
Mean				66.16	60.72	1.68	5.66	3.124	223.96	17.76	0.574
Std Dev				13.69	13.91	0.31	0.30	0.398	24.08	1.09	0.065
86D00758	F	1.0 mg/kg	28	85.6	149.6	1.6	6.3	3.39	252.1	22.5	0.31
86D00781	F	1.0 mg/kg	28	69.8	52.5	1.3	6.3	3.43	238.3	18.9	0.61
86D00799	F	1.0 mg/kg	28	73.5	38.1	2.2	6.4	3.58	252.2	15.6	0.61
86D00829	F	1.0 mg/kg	28	74.6	53.6	3.9	5.7	3.15	282.6	15.1	0.45
86D00837	F	1.0 mg/kg	28	50.5	NT	5.7	NT	NT	268.1	5.2	0.46
Mean				70.80	73.45	2.94	6.18	3.388	258.66	15.46	0.488
Std Dev				12.79	51.26	1.84	0.32	0.178	17.04	6.46	0.126
86D00759	F	10.0 mg/kg	28	82.2	83.9	1.7	6.4	3.59	214.9	14.5	0.65
86D00771	F	10.0 mg/kg	28	65.2	94.0	2.3	6.0	3.19	229.3	17.6	0.66
86D00789	F	10.0 mg/kg	28	81.4	152.3	1.9	6.2	3.39	212.4	24.0	0.60
86D00846	F	10.0 mg/kg	28	74.2	89.9	2.2	6.2	3.10	200.4	31.1	0.72
86D00852	F	10.0 mg/kg	28	62.7	104.5	3.2	5.7	3.23	281.2	18.7	0.53
Mean				73.14	104.92	2.26	6.10	3.300	227.64	21.18	0.632
Std Dev				8.99	27.53	0.58	0.26	0.193	31.65	6.52	0.071

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00785	F	30.0 mg/kg	28	81.5	96.7	2.2	6.5	3.26	232.2	20.9	0.69
86D00790	F	30.0 mg/kg	28	83.9	135.2	1.7	6.9	3.79	213.7	17.8	0.55
86D00794	F	30.0 mg/kg	28	78.3	44.9	1.8	6.1	3.51	216.9	20.6	0.64
86D00821	F	30.0 mg/kg	28	91.2	NT	1.8	5.6	3.01	209.5	19.5	0.41
86D00842	F	30.0 mg/kg	28	72.6	54.7	2.8	6.2	3.44	203.4	18.0	0.71
Mean				81.50	82.88	2.06	6.26	3.402	215.14	19.36	0.600
Std Dev				6.88	41.49	0.46	0.48	0.290	10.79	1.43	0.123
86D00775	F	60.0 mg/kg	28	90.8	56.8	2.3	6.4	3.21	213.9	19.9	0.66
86D00782	F	60.0 mg/kg	28	71.1	50.4	1.8	6.0	3.27	258.9	17.5	0.76
86D00797	F	60.0 mg/kg	28	70.9	62.1	2.8	6.0	3.21	266.3	13.5	0.55
86D00835	F	60.0 mg/kg	28	59.3	66.2	2.2	5.9	3.45	189.3	22.1	0.70
86D00841	F	60.0 mg/kg	28	51.7	58.8	1.7	5.9	3.34	185.5	17.9	0.59
Mean				68.76	58.86	2.16	6.04	3.296	222.78	18.18	0.652
Std Dev				14.80	5.92	0.44	0.21	0.101	38.04	3.19	0.084
86D00754	F	90.0 mg/kg	28	74.8	49.0	1.0	5.2	2.83	225.6	14.7	0.60
86D00757	F	90.0 mg/kg	28	68.6	63.9	3.8	6.2	3.28	256.4	13.0	0.52
86D00773	F	90.0 mg/kg	28	80.2	34.1	2.1	6.2	3.22	209.8	15.0	0.60
86D00779	F	90.0 mg/kg	28	74.4	74.7	2.2	6.3	3.73	195.5	19.8	0.64
86D00839	F	90.0 mg/kg	28	63.7	74.6	4.1	5.9	3.17	261.2	13.3	0.59
Mean				72.34	59.26	2.64	5.96	3.246	229.70	15.16	0.530
Std Dev				6.34	17.56	1.29	0.45	0.322	28.67	2.73	0.044

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00765	F	0 mg/kg	28	10.2	4.20	151	104	6.3	331	2.16
86D00814	F	0 mg/kg	28	9.7	5.20	143	101	5.2	325	2.40
86D00815	F	0 mg/kg	28	10.4	5.50	148	99	5.5	317	2.71
86D00825	F	0 mg/kg	28	11.3	6.90	152	102	5.8	422	2.63
86D00832	F	0 mg/kg	28	10.5	5.40	148	104	6.2	274	2.70
Mean				10.42	5.440	148.4	102.0	5.80	333.8	2.520
Std Dev				0.58	0.966	3.5	2.1	0.46	54.1	0.237
86D00758	F	1.0 mg/kg	28	10.9	7.60	152	102	6.3	NT	2.75
86D00781	F	1.0 mg/kg	28	9.9	6.60	144	99	6.0	201	2.39
86D00799	F	1.0 mg/kg	28	10.5	6.60	148	102	5.4	214	2.83
86D00829	F	1.0 mg/kg	28	11.9	7.00	153	106	7.4	335	3.16
86D00837	F	1.0 mg/kg	28	10.3	NT	NT	NT	NT	179	3.88
Mean				10.70	6.950	149.3	102.3	6.28	232.3	3.002
Std Dev				0.76	0.473	4.1	2.9	0.84	70.0	0.562
86D00759	F	10.0 mg/kg	28	9.8	5.20	142	96	5.6	215	2.63
86D00771	F	10.0 mg/kg	28	11.1	6.00	153	103	6.6	229	2.74
86D00789	F	10.0 mg/kg	28	11.2	7.40	149	98	6.5	272	2.84
86D00846	F	10.0 mg/kg	28	10.3	5.60	148	100	6.6	257	2.83
86D00852	F	10.0 mg/kg	28	11.5	5.10	154	108	6.8	304	3.25
Mean				10.78	5.860	149.2	101.0	6.42	255.4	2.858
Std Dev				0.70	0.932	4.8	4.7	0.47	35.2	0.235

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00785	F	30.0 mg/kg	28	11.0	8.40	145	98	6.2	271	2.65
86D00790	F	30.0 mg/kg	28	11.5	7.30	152	102	5.5	247	2.85
86D00794	F	30.0 mg/kg	28	10.3	9.40	145	101	6.7	232	2.48
86D00821	F	30.0 mg/kg	28	10.9	NT	159	108	5.6	276	2.67
86D00842	F	30.0 mg/kg	28	11.1	6.90	150	104	5.4	223	2.54
Mean				10.96	8.000	150.2	102.6	5.88	249.8	2.638
Std Dev				0.43	1.128	5.8	3.7	0.55	23.3	0.142
86D00775	F	60.0 mg/kg	28	11.0	9.20	149	107	7.2	210	3.14
86D00782	F	60.0 mg/kg	28	10.0	8.00	145	103	6.4	207	2.72
86D00797	F	60.0 mg/kg	28	10.8	8.60	141	99	5.4	159	2.47
86D00835	F	60.0 mg/kg	28	9.8	6.60	150	103	5.2	302	2.65
86D00841	F	60.0 mg/kg	28	10.1	6.90	150	103	5.0	233	2.66
Mean				10.34	7.860	147.0	103.0	5.84	222.2	2.728
Std Dev				0.53	1.104	3.9	2.8	0.93	52.1	0.249
86D00754	F	90.0 mg/kg	28	10.3	9.30	145	103	5.8	235	2.36
86D00757	F	90.0 mg/kg	28	11.4	10.10	152	104	6.3	168	3.01
86D00773	F	90.0 mg/kg	28	9.8	7.80	140	103	5.3	231	2.58
86D00779	F	90.0 mg/kg	28	10.0	8.30	148	105	6.7	270	2.57
86D00839	F	90.0 mg/kg	28	11.5	10.20	154	113	7.3	413	3.14
Mean				10.60	9.140	147.8	105.6	6.28	263.4	2.732
Std Dev				0.80	1.069	5.6	4.2	0.78	91.4	0.328

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00530	M	0 mg/kg	90	1.467	0.226	369.0	460.1	171.7	1360.2	280.6	0.00
86D00539	M	0 mg/kg	90	1.914	0.292	120.1	198.1	230.5	1272.0	613.3	0.00
86D00557	M	0 mg/kg	90	1.564	0.245	39.2	107.5	82.2	424.8	481.8	0.00
86D00566	M	0 mg/kg	90	1.707	0.226	50.5	125.3	121.0	861.2	586.1	0.00
86D00577	M	0 mg/kg	90	1.943	0.454	85.3	160.1	231.8	1117.4	843.9	0.05
86D00618	M	0 mg/kg	90	1.672	0.324	57.3	118.3	102.5	1150.7	778.3	0.00
86D00635	M	0 mg/kg	90	1.446	0.324	84.7	133.0	188.3	943.6	796.5	0.00
86D00688	M	0 mg/kg	90	1.887	0.259	93.2	143.7	211.2	522.9	453.5	0.00
86D00706	M	0 mg/kg	90	1.269	0.203	51.8	101.5	124.3	1000.3	774.3	0.00
86D00707	M	0 mg/kg	90	1.599	0.277	41.0	96.6	166.2	739.5	692.0	0.00
Mean				1.6468	0.2830	99.21	164.42	162.97	939.26	630.03	0.005
Std Dev				0.2225	0.0728	98.34	108.24	53.53	307.70	181.82	0.016
86D00531	M	1.0 mg/kg	90	0.620	0.245	60.0	88.2	152.3	237.5	323.9	0.00
86D00600	M	1.0 mg/kg	90	1.063	0.235	50.8	97.0	218.8	502.3	231.3	0.00
86D00625	M	1.0 mg/kg	90	0.938	0.207	45.6	95.0	145.0	425.6	196.9	0.00
86D00628	M	1.0 mg/kg	90	1.234	0.425	358.3	1509.6	353.4	295.2	239.6	0.00
86D00634	M	1.0 mg/kg	90	1.453	0.184	64.9	127.9	179.7	749.0	476.6	0.00
86D00666	M	1.0 mg/kg	90	1.173	0.296	44.1	103.8	134.0	1090.2	572.2	0.00
86D00678	M	1.0 mg/kg	90	1.404	0.268	45.8	80.1	192.4	189.5	260.7	0.06
86D00694	M	1.0 mg/kg	90	1.058	0.175	54.6	110.6	154.4	605.9	628.2	0.00
86D00731	M	1.0 mg/kg	90	1.355	0.184	64.0	105.3	117.1	364.5	523.6	0.00
86D00734	M	1.0 mg/kg	90	1.186	0.193	60.8	116.8	223.8	534.4	534.0	0.01
Mean				1.1484	0.2412	84.89	243.43	187.09	499.41	398.70	0.007
Std Dev				0.2470	0.0760	96.38	445.10	68.20	269.55	163.79	0.019

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00511	M	10.0 mg/kg	90	0.998	0.118	85.7	113.6	201.0	773.6	843.3	0.00
86D00526	M	10.0 mg/kg	90	0.803	0.109	45.1	126.9	228.4	1098.2	1237.0	0.00
86D00544	M	10.0 mg/kg	90	0.992	0.157	36.2	110.5	135.4	1376.5	1364.3	0.00
86D00553	M	10.0 mg/kg	90	1.179	0.176	40.9	191.0	149.6	1567.5	2412.0	0.00
86D00581	M	10.0 mg/kg	90	1.061	0.176	78.9	118.3	229.2	898.5	644.5	0.00
86D00583	M	10.0 mg/kg	90	0.928	0.128	35.6	139.8	100.8	1619.1	1254.1	0.00
86D00696	M	10.0 mg/kg	90	0.681	0.128	45.2	145.8	81.4	1518.6	1476.4	0.03
86D00698	M	10.0 mg/kg	90	1.316	0.166	46.1	115.6	95.8	907.9	923.8	0.00
86D00717	M	10.0 mg/kg	90	0.981	0.138	51.8	100.6	109.8	721.3	559.5	0.06
86D00723	M	10.0 mg/kg	90	0.727	0.118	37.8	104.3	193.4	1099.0	514.8	0.11
Mean				0.9666	0.1414	50.33	126.64	152.48	1158.02	1122.97	0.020
Std Dev				0.1958	0.0253	17.65	26.84	56.51	338.87	568.54	0.037
86D00612	M	30.0 mg/kg	90	NT	NT	87.9	262.9	94.8	1835.3	6631.8	0.00
86D00626	M	30.0 mg/kg	90	0.408	0.178	49.5	116.7	183.8	845.7	461.9	0.00
86D00636	M	30.0 mg/kg	90	0.691	0.045	43.6	104.1	158.8	695.7	333.0	0.00
86D00639	M	30.0 mg/kg	90	0.336	0.074	56.3	125.0	230.2	369.6	807.4	0.00
86D00646	M	30.0 mg/kg	90	0.661	0.184	34.3	58.0	64.5	251.8	270.0	0.07
86D00655	M	30.0 mg/kg	90	0.622	0.166	51.0	123.4	113.4	763.8	2659.8	0.00
86D00675	M	30.0 mg/kg	90	0.534	0.082	42.0	105.2	191.3	230.0	465.7	0.00
86D00676	M	30.0 mg/kg	90	0.586	0.091	47.3	116.9	87.0	713.0	446.2	0.07
86D00703	M	30.0 mg/kg	90	0.522	0.091	41.5	93.5	90.6	744.6	514.9	0.00
86D00718	M	30.0 mg/kg	90	0.541	0.082	34.1	95.2	94.1	317.8	650.8	0.00
Mean				0.5546	0.1103	48.75	120.09	130.85	676.73	1324.15	0.014
Std Dev				0.1148	0.0513	15.44	53.86	55.79	469.99	1990.96	0.030

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00550	M	60.0 mg/kg	90	0.730	0.064	49.1	93.3	120.8	360.0	246.9	0.00
86D00570	M	60.0 mg/kg	90	0.616	0.074	43.3	86.7	113.5	418.5	202.1	0.00
86D00617	M	60.0 mg/kg	90	0.482	0.064	41.8	109.0	96.4	313.7	304.9	0.00
86D00632	M	60.0 mg/kg	90	0.745	0.131	74.7	247.9	96.5	1122.7	1014.4	0.00
86D00641	M	60.0 mg/kg	90	0.120	0.128	44.3	85.0	120.1	246.9	463.3	0.05
86D00684	M	60.0 mg/kg	90	0.188	0.128	37.2	88.4	75.7	234.2	461.8	0.04
86D00686	M	60.0 mg/kg	90	0.000	0.072	62.1	131.6	138.8	666.0	849.5	0.00
86D00689	M	60.0 mg/kg	90	0.000	0.091	33.6	103.1	129.6	495.8	690.9	0.00
86D00690	M	60.0 mg/kg	90	0.000	0.091	31.2	95.1	164.9	826.8	722.8	0.00
86D00699	M	60.0 mg/kg	90	0.000	0.082	178.5	654.8	17.1	2049.4	6919.0	0.00
Mean				0.2881	0.0925	59.58	169.49	107.34	673.40	1187.56	0.009
Std Dev				0.3196	0.0269	43.82	177.35	40.22	559.54	2031.49	0.019
86D00563	M	90.0 mg/kg	90	0.055	0.064	32.9	96.8	176.4	663.7	491.5	0.00
86D00565	M	90.0 mg/kg	90	0.367	0.064	67.5	146.5	119.0	925.2	506.4	0.00
86D00568	M	90.0 mg/kg	90	0.126	0.055	41.1	114.8	105.9	507.3	368.7	0.00
86D00607	M	90.0 mg/kg	90	0.000	0.055	48.2	136.4	174.7	1053.1	680.0	0.00
86D00630	M	90.0 mg/kg	90	0.332	0.063	40.6	77.8	163.8	145.6	262.5	0.00
86D00652	M	90.0 mg/kg	90	0.268	0.054	54.1	109.5	118.3	1049.6	766.9	0.00
86D00659	M	90.0 mg/kg	90	0.399	0.082	37.5	75.2	128.2	251.4	444.0	0.00
86D00679	M	90.0 mg/kg	90	0.126	0.091	40.9	81.2	92.7	762.9	700.6	0.00
86D00708	M	90.0 mg/kg	90	0.192	0.072	35.6	88.7	164.7	246.2	796.4	0.00
86D00728	M	90.0 mg/kg	90	0.000	0.072	46.0	76.4	139.7	119.2	198.4	0.00
Mean				0.1865	0.0672	44.44	100.33	138.34	572.42	521.54	0.000
Std Dev				0.1490	0.0122	10.22	25.72	30.05	369.55	209.48	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00530	M	0 mg/kg	90	62.9	181.2	2.2	6.1	2.83	206.6	23.9	0.51
86D00539	M	0 mg/kg	90	52.2	145.9	2.2	5.8	3.08	249.4	20.9	0.69
86D00557	M	0 mg/kg	90	62.2	277.3	1.1	6.2	3.23	253.5	22.1	0.63
86D00566	M	0 mg/kg	90	52.9	271.3	1.1	6.2	3.21	228.3	21.4	0.47
86D00577	M	0 mg/kg	90	79.0	251.3	1.0	6.2	3.16	209.9	22.8	0.60
86D00618	M	0 mg/kg	90	77.8	202.3	2.6	6.9	3.44	240.8	30.3	0.71
86D00635	M	0 mg/kg	90	69.4	213.4	1.7	6.3	3.43	225.4	23.9	0.76
86D00688	M	0 mg/kg	90	58.0	139.4	2.8	6.8	3.27	242.4	23.9	0.60
86D00706	M	0 mg/kg	90	40.5	175.0	1.0	6.2	3.21	239.2	19.0	0.62
86D00707	M	0 mg/kg	90	36.4	93.5	1.2	5.3	2.83	231.6	22.1	0.62
Mean				59.13	195.06	1.69	6.20	3.169	232.71	23.03	0.621
Std Dev				14.24	60.14	0.70	0.45	0.210	15.59	2.99	0.087
86D00531	M	1.0 mg/kg	90	64.8	159.8	1.4	6.0	3.48	324.0	21.9	0.74
86D00600	M	1.0 mg/kg	90	73.4	347.0	1.0	6.6	3.01	177.0	20.2	0.59
86D00625	M	1.0 mg/kg	90	49.6	246.5	1.3	5.7	3.31	205.2	20.8	0.59
86D00628	M	1.0 mg/kg	90	94.2	120.1	1.7	5.4	3.23	80.5	34.4	0.66
86D00634	M	1.0 mg/kg	90	72.7	170.3	3.0	7.4	3.80	214.6	21.1	0.59
86D00666	M	1.0 mg/kg	90	60.8	96.6	1.3	6.4	3.20	268.6	23.7	0.56
86D00678	M	1.0 mg/kg	90	74.5	128.2	2.0	5.5	3.18	213.9	22.7	0.75
86D00694	M	1.0 mg/kg	90	37.4	154.0	1.0	5.7	3.08	273.1	20.1	0.59
86D00731	M	1.0 mg/kg	90	46.2	120.8	2.1	6.0	3.13	197.1	23.0	0.64
86D00734	M	1.0 mg/kg	90	57.4	193.7	2.6	6.4	3.20	262.4	24.3	0.64
Mean				63.10	173.70	1.74	6.11	3.262	221.64	23.22	0.635
Std Dev				16.55	74.54	0.68	0.61	0.228	66.57	4.19	0.066

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00511	M	10.0 mg/kg	90	70.7	219.6	2.6	6.6	3.07	299.1	23.0	0.56
86D00526	M	10.0 mg/kg	90	75.7	77.6	2.6	7.2	3.91	240.0	22.5	0.80
86D00544	M	10.0 mg/kg	90	52.1	170.0	0.9	5.9	3.29	208.4	19.6	0.58
86D00553	M	10.0 mg/kg	90	81.4	306.4	1.2	5.9	3.12	213.5	23.9	0.46
86D00581	M	10.0 mg/kg	90	82.8	201.3	1.8	6.8	3.62	219.5	20.7	0.72
86D00583	M	10.0 mg/kg	90	76.2	170.3	1.2	6.6	3.47	259.1	24.4	0.63
86D00696	M	10.0 mg/kg	90	47.5	175.9	1.4	6.6	3.38	239.4	18.2	0.61
86D00698	M	10.0 mg/kg	90	63.4	235.3	3.4	7.1	3.67	253.2	20.6	0.64
86D00717	M	10.0 mg/kg	90	72.3	97.5	1.3	6.0	3.19	188.7	18.9	0.77
86D00723	M	10.0 mg/kg	90	62.3	201.3	1.9	6.4	3.44	240.6	15.1	0.58
Mean				68.44	185.52	1.83	6.51	3.416	236.15	20.69	0.635
Std Dev				11.91	65.58	0.80	0.47	0.264	30.98	2.88	0.103
86D00612	M	30.0 mg/kg	90	50.8	244.0	1.6	5.6	3.12	233.8	17.8	0.55
86D00626	M	30.0 mg/kg	90	66.7	413.8	1.7	6.2	4.19	255.0	24.0	0.83
86D00636	M	30.0 mg/kg	90	62.6	129.4	1.0	5.6	3.33	231.0	20.5	0.71
86D00639	M	30.0 mg/kg	90	67.5	202.4	1.5	6.4	3.38	248.0	17.5	0.65
86D00646	M	30.0 mg/kg	90	57.7	159.9	3.1	6.4	3.51	245.7	18.3	0.61
86D00655	M	30.0 mg/kg	90	56.6	220.3	2.0	6.2	3.29	236.9	21.1	0.39
86D00675	M	30.0 mg/kg	90	88.3	176.9	1.5	6.7	3.64	225.2	23.3	0.65
86D00676	M	30.0 mg/kg	90	50.0	131.4	2.2	7.0	3.74	254.3	20.3	0.73
86D00703	M	30.0 mg/kg	90	84.5	325.9	2.2	6.5	2.98	217.6	19.4	0.59
86D00718	M	30.0 mg/kg	90	65.4	242.5	1.1	5.7	3.09	266.4	22.3	0.59
Mean				65.01	224.65	1.79	6.23	3.427	241.39	20.45	0.630
Std Dev				12.86	89.12	0.62	0.47	0.361	15.11	2.26	0.118

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00550	M	60.0 mg/kg	90	70.7	279.3	1.1	6.7	3.51	237.7	17.1	0.54
86D00570	M	60.0 mg/kg	90	60.5	156.4	1.5	6.7	3.23	237.0	19.0	0.69
86D00617	M	60.0 mg/kg	90	52.0	164.5	3.1	6.2	3.29	304.2	17.6	0.72
86D00632	M	60.0 mg/kg	90	65.7	75.9	1.0	5.9	3.24	210.2	15.5	0.52
86D00641	M	60.0 mg/kg	90	50.6	164.3	1.4	6.2	3.28	256.1	19.7	0.78
86D00684	M	60.0 mg/kg	90	41.1	168.5	2.4	6.3	3.50	227.3	19.6	0.67
86D00686	M	60.0 mg/kg	90	54.3	236.2	0.9	6.7	2.96	295.3	17.4	0.80
86D00689	M	60.0 mg/kg	90	56.4	323.2	2.4	6.9	3.20	279.7	16.2	0.54
86D00690	M	60.0 mg/kg	90	61.7	426.4	0.6	5.8	3.65	219.7	13.3	0.52
86D00699	M	60.0 mg/kg	90	45.2	NT	8.4	5.7	3.01	425.1	17.3	0.57
Mean				55.82	221.63	2.28	6.31	3.287	269.23	17.27	0.635
Std Dev				9.13	106.45	2.29	0.43	0.217	63.43	1.96	0.110
86D00563	M	90.0 mg/kg	90	72.5	486.3	0.6	6.7	3.68	213.5	16.4	0.53
86D00565	M	90.0 mg/kg	90	53.2	122.8	2.1	5.7	3.28	198.8	22.9	0.57
86D00568	M	90.0 mg/kg	90	64.1	349.6	2.8	5.8	3.27	331.5	17.0	0.68
86D00607	M	90.0 mg/kg	90	71.4	290.5	1.7	6.3	3.34	228.9	18.2	0.60
86D00630	M	90.0 mg/kg	90	52.9	147.3	1.6	6.3	3.44	238.0	21.9	0.77
86D00652	M	90.0 mg/kg	90	65.0	275.2	1.7	5.7	3.18	232.6	23.1	0.63
86D00659	M	90.0 mg/kg	90	56.4	100.5	2.8	5.5	3.14	268.1	20.5	0.73
86D00679	M	90.0 mg/kg	90	73.1	243.9	0.9	5.8	3.09	198.7	17.3	0.59
86D00708	M	90.0 mg/kg	90	58.6	182.1	1.3	5.6	2.93	196.2	17.0	0.60
86D00728	M	90.0 mg/kg	90	34.3	233.7	2.6	5.9	3.38	221.1	17.2	0.60
Mean				60.15	243.19	1.81	5.93	3.273	232.74	19.15	0.630
Std Dev				11.89	116.22	0.77	0.38	0.207	41.09	2.67	0.075

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00530	M	0 mg/kg	90	10.0	8.51	138	103	6.3	164	2.45
86D00539	M	0 mg/kg	90	9.9	7.57	144	104	6.9	165	2.50
86D00557	M	0 mg/kg	90	10.7	6.58	147	101	6.4	125	2.10
86D00566	M	0 mg/kg	90	10.5	7.45	141	102	6.3	173	2.37
86D00577	M	0 mg/kg	90	10.8	7.07	142	95	5.9	195	2.25
86D00618	M	0 mg/kg	90	11.3	5.93	140	104	5.8	200	2.76
86D00635	M	0 mg/kg	90	10.5	6.07	144	104	5.0	180	2.45
86D00688	M	0 mg/kg	90	11.1	6.10	138	105	5.9	171	2.76
86D00706	M	0 mg/kg	90	9.8	6.10	133	103	4.6	177	2.51
86D00707	M	0 mg/kg	90	8.7	5.32	142	93	5.4	165	2.46
Mean				10.33	6.670	140.9	101.4	5.85	171.5	2.461
Std Dev				0.76	0.963	3.9	4.1	0.69	20.5	0.202
86D00531	M	1.0 mg/kg	90	10.7	8.62	145	104	6.8	193	2.36
86D00600	M	1.0 mg/kg	90	11.0	8.47	150	96	6.0	149	2.30
86D00625	M	1.0 mg/kg	90	10.5	6.98	148	103	5.6	194	2.11
86D00628	M	1.0 mg/kg	90	10.6	6.97	145	109	5.3	350	2.48
86D00634	M	1.0 mg/kg	90	12.4	7.54	136	107	5.7	199	2.95
86D00666	M	1.0 mg/kg	90	10.5	4.94	145	104	6.8	155	2.56
86D00678	M	1.0 mg/kg	90	9.6	5.70	138	95	5.6	135	2.45
86D00694	M	1.0 mg/kg	90	9.9	6.53	140	98	5.5	155	2.60
86D00731	M	1.0 mg/kg	90	10.7	7.34	140	105	5.5	211	2.51
86D00734	M	1.0 mg/kg	90	11.0	6.09	136	100	5.7	153	2.67
Mean				10.69	6.918	142.3	102.1	5.85	189.4	2.499
Std Dev				0.75	1.160	5.0	4.7	0.53	62.1	0.226

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00511	M	10.0 mg/kg	90	11.0	7.16	146	102	6.3	152	3.06
86D00526	M	10.0 mg/kg	90	12.8	10.06	146	114	6.6	186	3.24
86D00544	M	10.0 mg/kg	90	10.2	4.81	139	103	5.3	118	2.31
86D00553	M	10.0 mg/kg	90	10.9	6.00	145	103	5.7	165	2.46
86D00581	M	10.0 mg/kg	90	11.5	7.43	142	107	5.6	154	2.73
86D00583	M	10.0 mg/kg	90	11.4	7.06	139	98	5.4	133	2.43
86D00696	M	10.0 mg/kg	90	10.9	5.56	141	103	5.3	148	2.31
86D00698	M	10.0 mg/kg	90	12.5	7.76	140	111	6.6	255	3.08
86D00717	M	10.0 mg/kg	90	10.9	8.00	137	99	5.1	145	2.58
86D00723	M	10.0 mg/kg	90	11.0	7.24	126	101	5.0	132	2.52
Mean				11.31	7.108	140.1	104.1	5.69	158.8	2.672
Std Dev				0.79	1.452	5.9	5.1	0.60	38.7	0.340
86D00612	M	30.0 mg/kg	90	10.2	8.40	147	105	6.7	175	2.71
86D00626	M	30.0 mg/kg	90	10.5	7.95	145	102	6.6	159	2.47
86D00636	M	30.0 mg/kg	90	10.1	6.77	145	104	5.2	120	2.36
86D00639	M	30.0 mg/kg	90	10.2	8.20	143	101	5.6	144	2.46
86D00646	M	30.0 mg/kg	90	12.1	7.39	136	107	5.6	116	2.66
86D00655	M	30.0 mg/kg	90	10.7	7.01	144	109	6.1	171	2.49
86D00675	M	30.0 mg/kg	90	12.0	6.38	144	107	5.4	178	2.38
86D00676	M	30.0 mg/kg	90	12.1	6.85	141	106	4.9	176	2.58
86D00703	M	30.0 mg/kg	90	11.1	7.32	135	102	5.4	160	2.83
86D00718	M	30.0 mg/kg	90	10.7	6.22	143	103	6.0	126	2.29
Mean				10.97	7.249	142.3	104.6	5.75	152.5	2.523
Std Dev				0.81	0.746	3.9	2.6	0.59	24.3	0.170

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00550	M	60.0 mg/kg	90	10.7	8.52	136	105	6.0	155	1.96
86D00570	M	60.0 mg/kg	90	10.5	7.72	145	101	5.5	115	2.21
86D00617	M	60.0 mg/kg	90	10.7	7.56	147	110	6.3	156	2.66
86D00632	M	60.0 mg/kg	90	10.3	8.46	145	108	6.3	126	2.05
86D00641	M	60.0 mg/kg	90	11.9	7.88	141	109	5.0	177	2.49
86D00684	M	60.0 mg/kg	90	11.8	8.41	146	108	5.4	180	2.41
86D00686	M	60.0 mg/kg	90	10.5	7.35	138	101	5.5	119	2.28
86D00689	M	60.0 mg/kg	90	11.3	7.64	142	108	6.2	92	2.70
86D00690	M	60.0 mg/kg	90	11.3	8.41	139	98	5.0	161	2.44
86D00699	M	60.0 mg/kg	90	13.6	16.87	NT	111	NT	165	3.51
Mean				11.26	8.882	142.1	105.9	5.69	144.6	2.471
Std Dev				0.99	2.839	3.9	4.4	0.53	29.6	0.437
86D00563	M	90.0 mg/kg	90	11.2	8.63	142	111	6.2	143	2.21
86D00565	M	90.0 mg/kg	90	10.2	7.66	142	111	6.0	145	2.07
86D00568	M	90.0 mg/kg	90	10.4	8.39	144	107	6.1	125	2.53
86D00607	M	90.0 mg/kg	90	11.0	6.66	140	109	5.2	165	2.54
86D00630	M	90.0 mg/kg	90	11.9	6.33	146	113	5.8	426	2.54
86D00652	M	90.0 mg/kg	90	9.9	6.77	145	99	5.5	166	2.41
86D00659	M	90.0 mg/kg	90	10.8	7.84	138	105	5.6	160	2.46
86D00679	M	90.0 mg/kg	90	10.1	6.68	141	102	5.2	153	1.92
86D00708	M	90.0 mg/kg	90	10.7	7.00	149	103	5.2	139	2.03
86D00728	M	90.0 mg/kg	90	11.3	7.72	139	112	5.7	164	2.41
Mean				10.75	7.368	142.6	107.2	5.65	178.6	2.312
Std Dev				0.62	0.790	3.4	4.8	0.38	87.9	0.234

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00768	F	0 mg/kg	90	1.106	1.606	89.6	174.8	140.8	456.3	554.9	0.00
86D00772	F	0 mg/kg	90	0.809	0.803	41.7	120.7	141.9	574.7	547.1	0.00
86D00776	F	0 mg/kg	90	1.122	1.817	43.8	93.8	104.3	351.3	342.4	0.00
86D00778	F	0 mg/kg	90	1.387	0.497	43.0	109.8	75.0	1275.2	906.0	0.00
86D00806	F	0 mg/kg	90	0.859	1.109	97.0	323.9	110.8	688.8	984.2	0.00
86D00810	F	0 mg/kg	90	0.791	1.243	42.9	108.1	118.0	646.6	614.2	0.00
86D00818	F	0 mg/kg	90	1.416	1.080	118.9	263.5	44.8	587.4	975.7	0.00
86D00833	F	0 mg/kg	90	1.151	0.918	38.0	140.7	59.1	1365.1	1084.4	0.00
86D00843	F	0 mg/kg	90	1.336	0.592	29.0	91.1	89.9	549.9	419.0	0.00
86D00849	F	0 mg/kg	90	0.259	1.118	50.3	147.4	99.4	609.6	578.4	0.01
Mean				1.0236	1.0783	59.42	157.38	98.40	710.49	700.63	0.001
Std Dev				0.3541	0.4123	30.60	77.56	32.15	335.85	262.55	0.003
86D00752	F	1.0 mg/kg	90	0.870	1.240	63.8	123.5	98.2	479.3	638.2	0.00
86D00755	F	1.0 mg/kg	90	1.475	0.606	31.8	129.4	85.5	942.5	805.7	0.00
86D00764	F	1.0 mg/kg	90	0.218	1.221	34.4	112.4	113.2	721.8	651.3	0.00
86D00774	F	1.0 mg/kg	90	0.141	1.016	34.5	82.8	121.3	478.6	664.0	0.00
86D00795	F	1.0 mg/kg	90	0.000	0.908	43.7	82.0	66.3	294.7	386.0	0.00
86D00804	F	1.0 mg/kg	90	0.000	0.889	46.0	127.8	49.9	635.4	684.1	0.02
86D00838	F	1.0 mg/kg	90	0.000	1.035	51.9	117.1	60.6	273.4	369.5	0.02
86D00840	F	1.0 mg/kg	90	0.000	0.840	86.6	180.5	95.2	641.4	873.4	0.01
86D00850	F	1.0 mg/kg	90	0.000	0.547	44.2	114.1	142.0	505.3	516.5	0.00
86D00855	F	1.0 mg/kg	90	0.000	1.114	42.4	211.7	55.3	1085.7	3868.3	0.00
Mean				0.2704	0.9416	47.93	128.13	88.75	605.81	945.70	0.005
Std Dev				0.5021	0.2342	16.51	40.14	30.84	260.09	1039.49	0.008

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00749	F	10.0 mg/kg	90	0.222	0.752	53.8	129.6	156.7	541.4	2092.8	0.00
86D00751	F	10.0 mg/kg	90	0.909	0.820	36.3	105.6	73.0	421.9	851.4	0.00
86D00753	F	10.0 mg/kg	90	0.813	0.342	35.4	87.3	92.4	291.7	340.0	0.00
86D00761	F	10.0 mg/kg	90	0.000	0.527	39.2	239.6	78.4	1373.2	1691.0	0.00
86D00784	F	10.0 mg/kg	90	0.000	1.055	33.8	143.5	157.6	845.9	565.7	0.00
86D00802	F	10.0 mg/kg	90	0.000	0.701	37.8	76.0	52.1	264.8	278.3	0.00
86D00803	F	10.0 mg/kg	90	0.000	0.869	42.2	94.1	126.3	470.3	484.3	0.00
86D00805	F	10.0 mg/kg	90	0.279	1.358	43.1	97.3	77.3	707.7	638.2	0.00
86D00826	F	10.0 mg/kg	90	0.000	0.664	96.2	116.4	96.4	224.9	408.0	0.00
86D00827	F	10.0 mg/kg	90	0.000	0.781	35.2	101.4	84.8	289.8	359.2	0.00
Mean				0.2223	0.7869	45.30	119.08	99.50	543.16	770.89	0.000
Std Dev				0.3528	0.2779	18.81	46.78	35.79	354.95	621.10	0.000
86D00766	F	30.0 mg/kg	90	0.000	0.172	31.9	85.1	150.6	416.9	366.2	0.00
86D00780	F	30.0 mg/kg	90	0.419	0.334	31.1	83.5	172.5	389.4	365.9	0.00
86D00787	F	30.0 mg/kg	90	0.283	0.573	51.4	132.1	144.8	812.8	576.9	0.00
86D00793	F	30.0 mg/kg	90	0.245	0.540	77.9	167.9	112.3	854.4	788.4	0.00
86D00811	F	30.0 mg/kg	90	0.000	0.363	44.2	138.1	134.0	1185.5	998.3	0.00
86D00812	F	30.0 mg/kg	90	0.678	0.545	40.1	115.1	70.4	530.4	497.6	0.00
86D00844	F	30.0 mg/kg	90	0.000	0.975	114.4	365.3	153.9	687.6	857.8	0.00
86D00848	F	30.0 mg/kg	90	0.149	0.879	44.0	120.7	152.5	315.9	427.5	0.00
86D00851	F	30.0 mg/kg	90	0.000	0.248	46.1	151.3	151.7	782.1	787.8	0.00
86D00854	F	30.0 mg/kg	90	0.000	0.659	45.0	95.5	65.2	503.8	382.8	0.00
Mean				0.1774	0.5288	52.61	145.46	130.79	647.88	604.92	0.000
Std Dev				0.2316	0.2609	25.28	82.07	36.62	267.38	234.06	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	ACHE	CHE	ALT	AST	ALK	LDH	CK	BILI
86D00760	F	60.0 mg/kg	90	0.138	0.420	50.1	145.7	67.5	868.1	603.7	0.00
86D00762	F	60.0 mg/kg	90	0.201	0.248	35.2	99.8	115.6	577.6	473.9	0.00
86D00769	F	60.0 mg/kg	90	0.000	0.286	73.3	201.1	114.6	575.5	474.8	0.00
86D00770	F	60.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT
86D00819	F	60.0 mg/kg	90	0.000	0.191	78.0	149.1	72.1	523.9	432.7	0.00
86D00820	F	60.0 mg/kg	90	0.265	0.258	37.3	112.1	70.2	268.2	258.3	0.00
86D00831	F	60.0 mg/kg	90	0.443	0.832	32.8	80.6	106.3	151.3	323.0	0.00
86D00845	F	60.0 mg/kg	90	0.000	0.401	118.6	216.0	86.6	993.2	580.1	0.00
86D00847	F	60.0 mg/kg	90	0.294	0.755	39.5	142.9	107.4	488.6	753.6	0.00
86D00856	F	60.0 mg/kg	90	0.000	0.774	32.7	112.9	112.2	493.8	532.7	0.00
Mean				0.1490	0.4628	55.28	140.02	94.72	548.91	492.53	0.000
Std Dev				0.1630	0.2543	29.30	45.13	20.47	261.01	149.01	0.000
86D00750	F	90.0 mg/kg	90	0.391	0.469	75.5	229.5	77.6	643.9	1342.8	0.00
86D00783	F	90.0 mg/kg	90	0.077	0.791	67.5	160.0	58.6	445.3	372.8	0.00
86D00792	F	90.0 mg/kg	90	0.000	0.313	90.8	254.8	87.9	941.6	2250.0	0.00
86D00798	F	90.0 mg/kg	90	0.000	0.234	63.1	116.0	77.6	229.3	259.3	0.00
86D00809	F	90.0 mg/kg	90	0.000	0.195	82.9	274.9	162.1	1146.7	1492.4	0.00
86D00813	F	90.0 mg/kg	90	0.000	0.352	34.6	111.5	95.3	443.9	520.9	0.00
86D00816	F	90.0 mg/kg	90	0.000	0.400	41.6	105.0	50.1	487.4	582.1	0.00
86D00817	F	90.0 mg/kg	90	0.000	0.332	45.6	123.2	107.4	511.7	1102.9	0.00
86D00822	F	90.0 mg/kg	90	0.000	0.410	46.2	95.8	64.2	290.8	276.7	0.00
86D00830	F	90.0 mg/kg	90	0.000	0.303	29.2	142.5	80.1	487.4	764.1	0.00
Mean				0.0468	0.3799	57.70	161.32	86.09	562.80	896.40	0.000
Std Dev				0.1233	0.1657	21.23	66.75	31.68	282.48	645.56	0.000

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00768	F	0 mg/kg	90	82.4	107.5	2.6	7.2	4.19	217.9	23.1	0.78
86D00772	F	0 mg/kg	90	64.4	142.9	2.6	6.2	3.74	262.1	22.8	0.75
86D00776	F	0 mg/kg	90	57.2	74.2	2.5	6.7	4.48	195.7	14.7	0.73
86D00778	F	0 mg/kg	90	88.8	53.1	2.9	6.2	3.90	250.4	19.2	0.86
86D00806	F	0 mg/kg	90	115.7	136.5	1.7	7.3	4.59	206.2	21.9	0.73
86D00810	F	0 mg/kg	90	98.5	215.7	2.1	7.6	4.48	179.8	18.2	0.80
86D00818	F	0 mg/kg	90	62.7	72.8	3.4	6.8	3.96	275.8	14.6	0.67
86D00833	F	0 mg/kg	90	49.4	147.8	1.9	6.8	3.59	236.8	13.5	0.76
86D00843	F	0 mg/kg	90	68.0	89.9	0.8	5.9	3.50	176.1	16.4	0.52
86D00849	F	0 mg/kg	90	62.9	204.7	3.9	7.7	3.78	231.2	17.3	0.69
Mean				75.00	124.51	2.44	6.84	4.021	223.20	18.17	0.729
Std Dev				20.78	55.34	0.88	0.61	0.392	34.07	3.52	0.091
86D00752	F	1.0 mg/kg	90	57.8	97.3	2.2	6.7	3.60	196.1	22.6	0.77
86D00755	F	1.0 mg/kg	90	72.1	67.1	1.0	6.0	3.44	211.0	18.0	0.61
86D00764	F	1.0 mg/kg	90	56.8	288.4	2.6	6.8	3.84	221.3	21.3	0.61
86D00774	F	1.0 mg/kg	90	66.9	214.8	2.3	6.7	3.89	252.2	21.1	0.75
86D00795	F	1.0 mg/kg	90	63.4	173.0	1.1	7.0	3.91	268.3	15.1	0.70
86D00804	F	1.0 mg/kg	90	64.8	93.3	1.8	6.8	3.92	204.1	16.1	0.73
86D00838	F	1.0 mg/kg	90	71.3	126.6	4.2	7.6	4.29	286.0	23.9	0.81
86D00840	F	1.0 mg/kg	90	59.7	196.5	2.4	7.0	4.20	196.4	20.7	0.67
86D00850	F	1.0 mg/kg	90	45.9	55.0	2.7	6.5	3.95	263.3	15.5	0.54
86D00855	F	1.0 mg/kg	90	49.5	76.0	1.6	5.5	3.62	240.8	16.8	0.50
Mean				60.82	138.80	2.19	6.66	3.866	233.95	19.11	0.669
Std Dev				8.65	76.52	0.92	0.57	0.262	32.58	3.18	0.102

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00749	F	10.0 mg/kg	90	62.9	108.0	1.3	6.0	3.75	170.5	18.5	0.57
86D00751	F	10.0 mg/kg	90	48.6	70.3	1.4	5.8	3.40	242.3	18.6	0.57
86D00753	F	10.0 mg/kg	90	71.1	111.9	2.7	6.2	3.63	251.3	24.2	0.75
86D00761	F	10.0 mg/kg	90	55.2	146.2	2.4	5.7	3.59	250.7	22.0	0.60
86D00784	F	10.0 mg/kg	90	42.5	40.3	1.4	5.6	2.03	131.7	20.7	0.52
86D00802	F	10.0 mg/kg	90	64.5	130.3	1.5	7.1	3.97	198.5	21.5	0.65
86D00803	F	10.0 mg/kg	90	75.5	146.0	2.2	7.0	4.28	225.9	21.6	0.62
86D00805	F	10.0 mg/kg	90	63.1	72.4	1.8	6.1	3.63	251.4	21.1	0.55
86D00826	F	10.0 mg/kg	90	82.2	97.1	1.5	6.2	3.66	224.0	22.4	0.66
86D00827	F	10.0 mg/kg	90	51.8	59.2	0.6	5.4	3.26	155.1	22.5	0.46
Mean				61.74	98.17	1.68	6.11	3.520	210.14	21.31	0.595
Std Dev				12.43	36.85	0.61	0.56	0.595	43.98	1.74	0.081
86D00766	F	30.0 mg/kg	90	52.3	257.0	2.1	6.8	3.38	248.2	16.4	0.65
86D00780	F	30.0 mg/kg	90	47.4	101.8	2.4	6.3	2.85	224.7	17.9	0.73
86D00787	F	30.0 mg/kg	90	51.2	71.9	1.9	6.4	3.49	231.1	16.7	0.71
86D00793	F	30.0 mg/kg	90	70.4	136.6	1.9	6.9	3.63	230.3	20.2	0.70
86D00811	F	30.0 mg/kg	90	65.2	109.9	1.9	6.5	3.30	177.4	18.0	0.57
86D00812	F	30.0 mg/kg	90	37.6	73.9	2.5	6.2	3.08	187.9	16.3	0.60
86D00844	F	30.0 mg/kg	90	79.7	96.8	3.7	7.2	3.84	212.7	19.9	0.58
86D00848	F	30.0 mg/kg	90	62.4	52.0	1.9	5.8	2.95	213.0	14.4	0.71
86D00851	F	30.0 mg/kg	90	59.9	109.0	2.1	6.0	3.18	284.6	22.0	0.68
86D00854	F	30.0 mg/kg	90	8.9	204.7	2.0	7.1	3.83	170.9	15.5	0.51
Mean				53.50	121.36	2.24	6.52	3.353	218.08	17.73	0.644
Std Dev				19.76	63.56	0.56	0.47	0.347	34.22	2.36	0.075

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CHOL	TRIG	URIC	TP	ALB	GLU	BUN	CR
86D00760	F	60.0 mg/kg	90	73.0	96.1	2.0	6.8	3.71	188.3	15.5	0.76
86D00762	F	60.0 mg/kg	90	69.9	118.3	2.0	6.0	3.35	211.3	22.1	0.59
86D00769	F	60.0 mg/kg	90	85.2	142.5	3.1	7.0	3.75	225.2	16.7	0.71
86D00770	F	60.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT
86D00819	F	60.0 mg/kg	90	66.5	128.1	1.3	6.5	3.57	222.6	13.8	0.49
86D00820	F	60.0 mg/kg	90	55.6	54.4	1.0	6.2	3.20	246.0	14.2	0.57
86D00831	F	60.0 mg/kg	90	56.7	39.7	2.1	6.4	3.26	211.8	12.8	0.75
86D00845	F	60.0 mg/kg	90	59.7	133.3	1.7	6.4	3.38	179.6	15.4	0.63
86D00847	F	60.0 mg/kg	90	69.8	60.5	2.1	6.7	3.68	204.5	18.0	0.74
86D00856	F	60.0 mg/kg	90	34.7	48.7	3.3	6.5	3.75	278.9	18.4	0.85
Mean				63.46	91.29	2.07	6.50	3.517	218.69	16.32	0.677
Std Dev				14.16	40.74	0.75	0.30	0.220	29.97	2.86	0.114
86D00750	F	90.0 mg/kg	90	71.7	91.5	2.3	6.5	3.95	228.2	21.3	0.71
86D00783	F	90.0 mg/kg	90	79.7	55.8	1.9	8.1	4.88	229.1	16.8	0.79
86D00792	F	90.0 mg/kg	90	60.0	NT	4.1	6.4	3.84	260.6	20.7	0.51
86D00798	F	90.0 mg/kg	90	73.4	76.2	1.0	6.1	3.65	229.8	16.5	0.69
86D00809	F	90.0 mg/kg	90	59.4	171.6	1.1	5.9	3.89	244.9	24.5	0.53
86D00813	F	90.0 mg/kg	90	75.3	30.5	2.0	6.4	3.72	208.1	17.6	0.70
86D00816	F	90.0 mg/kg	90	37.6	94.7	1.6	6.0	3.62	214.7	14.6	0.63
86D00817	F	90.0 mg/kg	90	53.5	159.4	3.9	6.6	4.16	258.9	23.2	0.69
86D00822	F	90.0 mg/kg	90	69.4	79.7	2.4	6.8	3.93	219.8	21.5	0.72
86D00830	F	90.0 mg/kg	90	57.0	59.3	1.4	5.8	3.58	211.5	14.4	0.53
Mean				63.70	90.97	2.17	6.46	3.922	230.56	19.11	0.650
Std Dev				12.66	46.69	1.07	0.66	0.381	18.72	3.59	0.096

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00768	F	0 mg/kg	90	11.0	3.76	143	104	5.2	420	2.52
86D00772	F	0 mg/kg	90	11.4	3.14	147	110	5.6	341	2.90
86D00776	F	0 mg/kg	90	10.5	3.83	145	110	5.6	396	2.51
86D00778	F	0 mg/kg	90	11.0	4.09	146	107	5.8	307	2.79
86D00806	F	0 mg/kg	90	11.0	6.13	148	105	5.1	451	2.32
86D00810	F	0 mg/kg	90	11.7	5.61	144	101	5.2	403	2.46
86D00818	F	0 mg/kg	90	10.5	6.60	141	104	7.8	255	2.97
86D00833	F	0 mg/kg	90	10.3	8.06	144	107	5.8	252	2.82
86D00843	F	0 mg/kg	90	10.6	6.26	139	104	5.4	299	2.25
86D00849	F	0 mg/kg	90	11.3	7.23	143	103	5.5	346	2.97
Mean				10.93	5.471	144.0	105.5	5.70	347.0	2.651
Std Dev				0.45	1.670	2.7	3.0	0.78	69.2	0.270
86D00752	F	1.0 mg/kg	90	10.4	5.52	149	101	6.5	421	2.48
86D00755	F	1.0 mg/kg	90	10.1	2.88	153	105	4.9	394	2.12
86D00764	F	1.0 mg/kg	90	10.7	5.07	151	102	6.1	303	2.68
86D00774	F	1.0 mg/kg	90	10.5	6.02	146	99	5.6	267	2.49
86D00795	F	1.0 mg/kg	90	10.4	5.16	145	99	5.8	206	2.21
86D00804	F	1.0 mg/kg	90	10.2	5.20	146	102	4.4	271	2.32
86D00838	F	1.0 mg/kg	90	12.5	8.99	159	109	6.7	229	2.83
86D00840	F	1.0 mg/kg	90	10.9	7.46	150	100	5.9	231	2.50
86D00850	F	1.0 mg/kg	90	10.9	8.00	149	103	7.1	270	2.70
86D00855	F	1.0 mg/kg	90	10.3	8.84	149	105	7.9	365	2.37
Mean				10.69	6.314	149.7	102.5	6.09	295.7	2.470
Std Dev				0.69	1.953	4.1	3.1	1.03	73.8	0.224

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00749	F	10.0 mg/kg	90	9.9	4.83	144	103	5.2	343	2.15
86D00751	F	10.0 mg/kg	90	9.8	3.91	142	102	5.1	371	2.22
86D00753	F	10.0 mg/kg	90	10.2	4.23	142	102	5.4	221	2.70
86D00761	F	10.0 mg/kg	90	9.8	6.00	145	107	6.9	314	2.92
86D00784	F	10.0 mg/kg	90	9.6	7.16	143	104	5.8	134	2.28
86D00802	F	10.0 mg/kg	90	11.1	6.31	142	105	4.6	292	2.13
86D00803	F	10.0 mg/kg	90	11.0	5.15	143	104	5.1	233	2.57
86D00805	F	10.0 mg/kg	90	10.4	5.73	145	105	5.2	301	2.34
86D00826	F	10.0 mg/kg	90	10.8	8.06	138	100	6.6	323	2.08
86D00827	F	10.0 mg/kg	90	9.9	6.65	141	108	4.9	273	1.69
Mean				10.25	5.803	142.5	104.0	5.48	280.5	2.308
Std Dev				0.55	1.307	2.1	2.4	0.74	69.0	0.349
86D00766	F	30.0 mg/kg	90	11.0	5.37	141	104	6.9	357	2.90
86D00780	F	30.0 mg/kg	90	10.2	3.92	139	106	5.1	304	2.57
86D00787	F	30.0 mg/kg	90	10.2	4.24	142	108	4.2	304	2.37
86D00793	F	30.0 mg/kg	90	11.2	5.27	140	104	5.5	310	2.52
86D00811	F	30.0 mg/kg	90	10.3	6.09	140	102	4.7	340	2.40
86D00812	F	30.0 mg/kg	90	10.3	6.04	140	106	7.3	326	2.72
86D00844	F	30.0 mg/kg	90	11.8	6.04	143	107	6.3	337	2.81
86D00848	F	30.0 mg/kg	90	9.9	2.45	140	108	4.9	307	2.29
86D00851	F	30.0 mg/kg	90	10.7	7.91	144	109	6.6	329	2.84
86D00854	F	30.0 mg/kg	90	11.1	6.89	142	102	4.8	373	2.59
Mean				10.67	5.422	141.1	105.6	5.63	328.7	2.611
Std Dev				0.59	1.566	1.6	2.5	1.07	23.6	0.210

Appendix M (cont.): SERUM CHEMISTRY

Animal	Sex	Group	Day	CAL	PHOS	NA	CL	K	IRON	MAG
86D00760	F	60.0 mg/kg	90	10.9	3.49	143	109	4.8	426	2.25
86D00762	F	60.0 mg/kg	90	11.7	4.74	144	108	4.8	302	2.60
86D00769	F	60.0 mg/kg	90	11.0	4.13	139	109	6.8	308	2.67
86D00770	F	60.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT
86D00819	F	60.0 mg/kg	90	10.9	5.07	140	111	5.1	275	2.44
86D00820	F	60.0 mg/kg	90	9.9	5.02	139	109	4.9	303	1.89
86D00831	F	60.0 mg/kg	90	10.9	5.86	140	104	4.8	262	2.33
86D00845	F	60.0 mg/kg	90	10.9	5.84	140	104	4.5	226	2.37
86D00847	F	60.0 mg/kg	90	10.6	4.43	142	110	4.3	254	2.31
86D00856	F	60.0 mg/kg	90	11.0	6.65	144	111	5.0	253	2.78
Mean				10.87	5.026	141.2	108.3	5.00	289.9	2.404
Std Dev				0.47	0.974	2.0	2.6	0.72	58.0	0.263
86D00750	F	90.0 mg/kg	90	10.6	5.35	146	111	5.5	224	2.53
86D00783	F	90.0 mg/kg	90	11.7	4.27	152	109	4.8	308	2.53
86D00792	F	90.0 mg/kg	90	11.3	6.86	144	113	7.6	297	3.02
86D00798	F	90.0 mg/kg	90	10.4	5.85	144	113	5.3	224	2.19
86D00809	F	90.0 mg/kg	90	10.7	7.27	142	112	6.5	362	2.52
86D00813	F	90.0 mg/kg	90	10.5	5.34	144	111	5.3	264	2.30
86D00816	F	90.0 mg/kg	90	9.1	4.28	125	97	4.8	230	2.32
86D00817	F	90.0 mg/kg	90	11.9	7.20	141	114	6.3	259	3.03
86D00822	F	90.0 mg/kg	90	10.9	7.18	144	111	5.6	235	2.66
86D00830	F	90.0 mg/kg	90	10.4	7.77	145	113	4.9	283	2.34
Mean				10.75	6.137	142.7	110.4	5.66	268.6	2.544
Std Dev				0.79	1.289	6.9	4.9	0.90	44.7	0.289

Appendix N: HEMATOLOGY

List of Hematology Abbreviations/Units

RBC	Erythrocytes ($x10^6/\mu l$)
HGB	Hemoglobin (g/dl)
HCT	Hematocrit (%)
MCV	Mean Corpuscular Volume (femtoliters)
MCH	Mean Corpuscular Hemoglobin (picograms)
MCHC	Mean Corpuscular Hemoglobin Concentration (g/dl)
RET	Reticulocytes (%)
PLT	Platelets ($x10^3/\mu l$)
WBC	Total Leukocyte Count ($x10^3/\mu l$)
SEG	Polymorphonuclear Granulocytes (%)
BAN	Immature Neutrophils (%)
EOS	Eosinophils (%)
BAS	Basophils (%)
LYM	Lymphocytes (%)
MON	Monocytes (%)
ATL	Atypical Lymphocytes (%)
NRBC	Nucleated Red Blood Cell (#/100 WBC)
NT	Not Taken

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00512	M	baseline	0	6.40	14.1	39.3	61	21.9	35.7	0.0	789
86D00519	M	baseline	0	6.08	13.5	37.3	61	22.1	35.9	0.4	895
86D00529	M	baseline	0	4.17	8.8	25.3	60	20.9	34.7	0.8	652
86D00564	M	baseline	0	6.14	14.0	39.0	63	22.7	35.9	0.6	1039
86D00637	M	baseline	0	6.46	14.5	40.2	62	22.4	36.0	0.6	962
86D00687	M	baseline	0	5.72	13.1	37.9	60	23.7	35.3	0.0	652
86D00673	M	baseline	0	6.21	13.4	38.6	59	22.3	34.4	0.2	618
86D00702	M	baseline	0	6.07	13.4	36.7	60	22.0	36.3	0.8	784
86D00711	M	baseline	0	5.65	12.8	37.2	63	22.9	34.6	0.4	878
86D00714	M	baseline	0	6.35	13.9	38.9	61	21.8	35.5	0.2	688
Mean				5.925	13.15	37.04	61.0	22.27	35.43	0.40	795.7
Std Dev				0.672	1.61	4.26	1.3	0.74	0.66	0.30	144.6
86D00756	F	baseline	0	5.62	12.8	34.4	61	22.6	36.9	1.8	750
86D00767	F	baseline	0	5.77	13.3	37.0	64	22.9	35.7	0.8	338
86D00777	F	baseline	0	6.06	13.6	37.6	62	22.3	36.0	2.2	525
86D00786	F	baseline	0	6.21	13.8	38.4	62	22.1	35.8	0.6	684
86D00791	F	baseline	0	6.60	15.4	41.7	63	23.2	36.8	0.6	400
86D00800	F	baseline	0	6.16	14.2	39.1	63	22.8	36.0	10.0	434
86D00807	F	baseline	0	6.42	14.7	40.8	63	22.7	35.8	3.2	777
86D00808	F	baseline	0	6.23	14.2	37.9	61	22.6	37.2	1.2	601
86D00823	F	baseline	0	6.25	14.2	39.2	62	22.6	36.0	1.2	454
86D00828	F	baseline	0	6.23	14.1	39.5	63	22.5	35.6	1.2	630
Mean				6.155	14.03	38.56	62.4	22.63	36.18	2.28	559.3
Std Dev				0.286	0.72	2.04	1.0	0.31	0.57	2.83	152.2

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00512	M	baseline	0	5.3	10	0	0	0	89	1	0	0
86D00519	M	baseline	0	2.5	21	0	0	0	79	0	0	0
86D00529	M	baseline	0	4.2	19	0	1	0	80	0	0	0
86D00564	M	baseline	0	3.2	9	0	0	0	91	0	0	0
86D00637	M	baseline	0	6.3	13	0	0	0	87	0	0	0
86D00687	M	baseline	0	6.0	27	0	0	0	73	0	0	0
86D00673	M	baseline	0	5.8	27	0	0	0	73	0	0	0
86D00702	M	baseline	0	6.3	8	0	0	0	91	1	0	0
86D00711	M	baseline	0	4.9	28	0	0	0	72	0	0	0
86D00714	M	baseline	0	6.5	8	0	1	0	90	1	0	0
Mean				5.10	17.0	0.0	0.2	0.0	82.5	0.3	0.0	0.0
Std Dev				1.39	8.4	0.0	0.4	0.0	8.0	0.5	0.0	0.0
86D00756	F	baseline	0	4.1	12	0	2	0	86	0	0	0
86D00767	F	baseline	0	2.4	9	0	0	0	91	0	0	0
86D00777	F	baseline	0	5.1	11	0	1	0	88	0	0	0
86D00786	F	baseline	0	4.6	13	0	0	0	87	0	0	0
86D00791	F	baseline	0	4.3	15	0	2	0	83	0	0	0
86D00800	F	baseline	0	6.6	11	0	2	0	87	0	0	0
86D00807	F	baseline	0	5.2	7	0	0	0	93	0	0	0
86D00808	F	baseline	0	2.6	20	0	1	0	79	0	0	0
86D00823	F	baseline	0	5.3	9	0	0	0	91	0	0	0
86D00828	F	baseline	0	4.5	22	0	0	0	78	0	0	0
Mean				4.47	12.9	0.0	0.8	0.0	86.3	0.0	0.0	0.0
Std Dev				1.25	4.8	0.0	0.9	0.0	5.0	0.0	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00543	M	0 mg/kg	28	6.96	14.9	41.3	59	21.1	24.3	0.0	644
86D00620	M	0 mg/kg	28	7.44	15.7	44.2	59	21.0	35.4	0.4	560
86D00680	M	0 mg/kg	28	7.70	15.9	44.8	58	20.6	35.3	0.4	574
86D00681	M	0 mg/kg	28	7.03	15.1	42.9	61	21.4	35.1	0.6	480
86D00712	M	0 mg/kg	28	7.22	15.4	42.1	58	21.2	36.3	0.4	680
Mean				7.270	15.40	43.06	59.0	21.06	33.28	0.36	587.6
Std Dev				0.304	0.41	1.45	1.2	0.30	5.04	0.22	77.9
86D00506	M	1.0 mg/kg	28	6.78	14.6	40.9	60	21.4	35.4	0.2	902
86D00507	M	1.0 mg/kg	28	7.87	15.9	45.1	57	20.2	35.1	0.2	720
86D00548	M	1.0 mg/kg	28	7.24	14.7	41.2	57	20.2	35.5	0.0	402
86D00606	M	1.0 mg/kg	28	7.53	16.2	45.7	61	21.3	35.2	0.6	512
86D00733	M	1.0 mg/kg	28	7.27	15.2	41.8	57	20.9	36.2	0.0	1108
Mean				7.338	15.32	42.94	58.4	20.80	35.48	0.20	728.8
Std Dev				0.402	0.71	2.28	1.9	0.58	0.43	0.24	286.2
86D00510	M	10.0 mg/kg	28	7.07	15.6	43.7	62	22.0	35.5	0.6	816
86D00520	M	10.0 mg/kg	28	4.61	10.5	27.3	59	22.6	38.2	0.2	398
86D00599	M	10.0 mg/kg	28	7.43	15.4	42.2	57	20.7	36.2	0.4	610
86D00602	M	10.0 mg/kg	28	7.38	15.5	43.7	59	20.9	35.2	0.0	548
86D00713	M	10.0 mg/kg	28	7.13	15.4	42.5	60	21.5	36.0	0.2	550
Mean				6.724	14.48	39.88	59.4	21.54	36.22	0.28	584.4
Std Dev				1.192	2.23	7.07	1.8	0.78	1.18	0.23	151.3

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00554	M	30.0 mg/kg	28	7.24	14.2	38.6	53	19.5	36.5	0.8	714
86D00593	M	30.0 mg/kg	28	7.13	15.5	43.6	61	21.6	35.3	0.0	816
86D00604	M	30.0 mg/kg	28	6.95	15.1	41.5	60	21.6	36.2	0.0	888
86D00644	M	30.0 mg/kg	28	7.52	15.7	43.4	58	20.7	35.9	0.2	952
86D00645	M	30.0 mg/kg	28	6.91	15.0	40.7	59	21.5	36.7	0.0	636
Mean				7.150	15.10	41.56	58.2	20.98	36.12	0.20	801.2
Std Dev				0.246	0.58	2.06	3.1	0.91	0.55	0.35	127.9
86D00509	M	60.0 mg/kg	28	6.33	15.7	43.4	59	21.3	36.0	0.0	604
86D00533	M	60.0 mg/kg	28	6.85	14.7	39.9	58	21.3	36.5	1.0	492
86D00621	M	60.0 mg/kg	28	6.62	14.5	38.9	59	21.8	37.0	0.0	612
86D00648	M	60.0 mg/kg	28	6.89	15.1	41.0	59	21.8	36.5	0.6	740
86D00726	M	60.0 mg/kg	28	7.74	15.9	43.1	56	20.4	36.6	0.0	762
Mean				6.886	15.18	41.26	58.2	21.32	36.52	0.32	642.0
Std Dev				0.527	0.61	1.97	1.3	0.57	0.36	0.46	110.5
86D00523	M	90.0 mg/kg	28	7.09	15.3	42.2	59	21.4	36.0	0.6	560
86D00552	M	90.0 mg/kg	28	7.58	15.7	43.5	57	20.7	36.0	0.0	888
86D00587	M	90.0 mg/kg	28	7.04	14.6	40.2	57	20.6	36.0	0.6	592
86D00631	M	90.0 mg/kg	28	7.53	15.0	41.5	55	19.8	36.0	0.8	504
86D00674	M	90.0 mg/kg	28	6.07	14.9	41.3	58	21.0	36.0	0.0	480
Mean				7.062	15.10	41.74	57.2	20.70	36.00	0.40	604.8
Std Dev				0.607	0.42	1.22	1.5	0.59	0.00	0.37	164.4

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00543	M	0 mg/kg	28	8.7	19	0	0	0	81	0	0	0
86D00620	M	0 mg/kg	28	8.8	8	0	0	0	92	0	0	0
86D00680	M	0 mg/kg	28	14.3	13	1	0	0	86	0	0	0
86D00681	M	0 mg/kg	28	8.8	41	0	0	0	59	0	0	0
86D00712	M	0 mg/kg	28	5.3	8	0	1	0	91	0	0	0
Mean				9.18	17.8	0.2	0.2	0.0	81.8	0.0	0.0	0.0
Std Dev				3.23	13.7	0.4	0.4	0.0	13.5	0.0	0.0	0.0
86D00506	M	1.0 mg/kg	28	2.9	15	0	0	0	85	0	0	0
86D00507	M	1.0 mg/kg	28	3.9	6	0	0	0	94	0	0	0
86D00548	M	1.0 mg/kg	28	9.1	23	0	1	0	76	0	0	0
86D00606	M	1.0 mg/kg	28	9.0	11	0	0	0	89	0	0	0
86D00733	M	1.0 mg/kg	28	7.5	8	0	1	0	89	0	2	0
Mean				6.48	12.6	0.0	0.4	0.0	86.6	0.0	0.4	0.0
Std Dev				2.90	6.7	0.0	0.5	0.0	6.7	0.0	0.9	0.0
86D00510	M	10.0 mg/kg	28	8.0	15	0	0	0	85	0	0	0
86D00520	M	10.0 mg/kg	28	2.4	14	1	0	0	85	0	0	0
86D00599	M	10.0 mg/kg	28	9.1	13	0	0	0	87	0	0	0
86D00602	M	10.0 mg/kg	28	6.9	16	0	1	0	83	0	0	0
86D00713	M	10.0 mg/kg	28	8.7	13	0	1	0	86	0	0	0
Mean				7.02	14.2	0.2	0.4	0.0	85.2	0.0	0.0	0.0
Std Dev				2.71	1.3	0.4	0.5	0.0	1.5	0.0	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00554	M	30.0 mg/kg	28	5.2	7	0	1	0	92	0	0	0
86D00593	M	30.0 mg/kg	28	12.0	5	0	0	0	95	0	0	0
86D00604	M	30.0 mg/kg	28	5.8	25	0	1	0	74	0	0	0
86D00644	M	30.0 mg/kg	28	7.4	3	0	0	0	97	0	0	0
86D00645	M	30.0 mg/kg	28	5.0	8	0	0	0	92	0	0	0
Mean				7.08	9.6	0.0	0.4	0.0	90.0	0.0	0.0	0.0
Std Dev				2.91	8.8	0.0	0.5	0.0	9.2	0.0	0.0	0.0
86D00509	M	60.0 mg/kg	28	5.5	18	0	1	0	81	0	0	0
86D00533	M	60.0 mg/kg	28	10.9	51	0	1	0	48	0	0	0
86D00621	M	60.0 mg/kg	28	4.2	11	0	0	0	89	0	0	0
86D00648	M	60.0 mg/kg	28	5.6	15	0	0	0	85	0	0	0
86D00726	M	60.0 mg/kg	28	2.7	14	0	1	0	85	0	0	0
Mean				5.78	21.8	0.0	0.6	0.0	77.6	0.0	0.0	0.0
Std Dev				3.09	16.5	0.0	0.5	0.0	16.8	0.0	0.0	0.0
86D00523	M	90.0 mg/kg	28	6.6	10	0	0	0	90	0	0	0
86D00552	M	90.0 mg/kg	28	5.8	6	0	0	0	94	0	0	0
86D00587	M	90.0 mg/kg	28	6.7	25	0	0	0	75	0	0	0
86D00631	M	90.0 mg/kg	28	3.3	19	0	0	0	81	0	0	0
86D00674	M	90.0 mg/kg	28	5.9	15	0	0	0	85	0	0	0
Mean				5.66	15.0	0.0	0.0	0.0	85.0	0.0	0.0	0.0
Std Dev				1.38	7.4	0.0	0.0	0.0	7.4	0.0	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00765	F	0 mg/kg	28	6.61	15.1	40.2	61	22.7	37.4	0.4	936
86D00814	F	0 mg/kg	28	4.25	9.1	23.6	55	21.1	38.2	0.4	1076
86D00815	F	0 mg/kg	28	6.83	14.7	37.8	55	21.5	38.8	0.2	946
86D00825	F	0 mg/kg	28	6.01	13.8	33.2	55	22.8	41.3	0.4	944
86D00832	F	0 mg/kg	28	7.17	15.3	40.1	56	21.2	37.8	0.4	762
Mean				6.174	13.60	34.98	56.4	21.86	38.70	0.36	932.8
Std Dev				1.156	2.58	6.97	2.6	0.83	1.54	0.09	111.8
86D00781	F	1.0 mg/kg	28	6.99	14.4	38.9	56	20.4	36.7	0.6	972
86D00758	F	1.0 mg/kg	28	6.68	14.7	37.7	56	21.9	38.7	0.2	786
86D00799	F	1.0 mg/kg	28	7.14	15.4	40.5	57	21.5	37.7	0.6	890
86D00829	F	1.0 mg/kg	28	7.05	16.0	42.5	60	22.7	37.6	0.6	858
86D00837	F	1.0 mg/kg	28	6.45	14.4	36.8	57	22.3	39.0	0.2	862
Mean				6.862	14.98	39.28	57.2	21.76	37.94	0.44	873.6
Std Dev				0.288	0.70	2.27	1.6	0.88	0.92	0.22	67.1
86D00759	F	10.0 mg/kg	28	6.80	14.1	38.4	56	20.7	36.6	0.4	980
86D00771	F	10.0 mg/kg	28	6.73	14.8	38.7	57	21.9	37.9	0.6	686
86D00789	F	10.0 mg/kg	28	6.70	14.5	38.5	57	21.5	37.4	0.6	822
86D00846	F	10.0 mg/kg	28	6.49	14.4	38.7	60	22.1	37.1	0.4	922
86D00852	F	10.0 mg/kg	28	6.91	15.1	41.0	59	21.8	36.6	0.6	998
Mean				6.726	14.58	39.06	57.8	21.60	37.12	0.52	881.6
Std Dev				0.155	0.38	1.09	1.6	0.55	0.55	0.11	129.1

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00785	F	30.0 mg/kg	28	6.95	14.9	38.8	56	21.3	38.1	0.0	894
86D00790	F	30.0 mg/kg	28	6.73	14.5	37.2	55	21.4	38.7	0.6	862
86D00794	F	30.0 mg/kg	28	7.56	15.4	40.1	53	20.3	38.2	0.4	1016
86D00821	F	30.0 mg/kg	28	7.38	16.4	44.9	61	22.2	36.5	1.2	904
86D00842	F	30.0 mg/kg	28	6.89	14.6	37.9	55	21.2	38.4	0.8	1086
Mean				7.102	15.16	39.78	56.0	21.28	37.98	0.60	952.4
Std Dev				0.351	0.78	3.06	3.0	0.68	0.86	0.45	94.6
86D00775	F	60.0 mg/kg	28	7.31	15.1	42.9	59	20.6	34.9	0.2	1012
86D00782	F	60.0 mg/kg	28	6.82	15.0	41.1	60	21.9	36.4	0.6	942
86D00797	F	60.0 mg/kg	28	6.60	15.1	39.9	60	22.7	37.6	0.6	868
86D00835	F	60.0 mg/kg	28	7.37	15.5	42.3	57	21.0	36.5	0.8	976
86D00841	F	60.0 mg/kg	28	6.25	13.5	35.2	56	21.6	38.2	0.6	838
Mean				6.870	14.84	40.28	58.4	21.56	36.72	0.56	927.2
Std Dev				0.475	0.77	3.06	1.8	0.81	1.27	0.22	72.9
86D00754	F	90.0 mg/kg	28	6.83	14.2	39.3	57	20.7	35.8	0.8	954
86D00757	F	90.0 mg/kg	28	6.93	15.5	42.3	61	22.2	36.4	1.0	964
86D00773	F	90.0 mg/kg	28	6.58	14.5	39.7	60	21.8	36.3	0.0	816
86D00779	F	90.0 mg/kg	28	6.44	14.2	37.4	58	21.8	37.7	0.6	842
86D00839	F	90.0 mg/kg	28	7.61	16.6	45.6	60	21.7	36.2	0.8	816
Mean				6.878	15.00	40.86	59.2	21.64	36.48	0.64	878.4
Std Dev				0.453	1.04	3.17	1.6	0.56	0.72	0.38	74.4

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00765	F	0 mg/kg	28	5.3	20	0	0	0	80	0	0	0
86D00814	F	0 mg/kg	28	2.6	7	0	0	0	93	0	0	0
86D00815	F	0 mg/kg	28	4.2	11	0	0	0	89	0	0	0
86D00825	F	0 mg/kg	28	3.6	13	0	0	0	87	0	0	0
86D00832	F	0 mg/kg	28	4.9	10	0	0	0	90	0	0	0
Mean				4.22	12.2	0.0	0.0	0.0	87.8	0.0	0.0	0.0
Std Dev				1.22	4.9	0.0	0.0	0.0	4.9	0.0	0.0	0.0
86D00781	F	1.0 mg/kg	28	7.2	2	0	2	0	96	0	0	0
86D00758	F	1.0 mg/kg	28	3.5	9	0	3	0	88	0	0	0
86D00799	F	1.0 mg/kg	28	4.4	23	0	0	0	77	0	0	0
86D00829	F	1.0 mg/kg	28	6.8	8	0	0	0	92	0	0	0
86D00837	F	1.0 mg/kg	28	2.6	14	0	0	0	86	0	0	0
Mean				4.90	11.2	0.0	1.0	0.0	87.8	0.0	0.0	0.0
Std Dev				2.02	7.9	0.0	1.4	0.0	7.2	0.0	0.0	0.0
86D00759	F	10.0 mg/kg	28	4.1	8	0	2	0	90	0	0	0
86D00771	F	10.0 mg/kg	28	4.8	10	0	0	0	90	0	0	0
86D00789	F	10.0 mg/kg	28	7.8	9	0	2	0	89	0	0	0
86D00846	F	10.0 mg/kg	28	5.6	16	0	0	0	84	0	0	0
86D00852	F	10.0 mg/kg	28	5.3	9	0	1	0	89	0	0	0
Mean				5.52	10.4	0.0	1.0	0.0	88.4	0.0	0.0	0.0
Std Dev				1.40	3.2	0.0	1.0	0.0	2.5	0.0	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00785	F	30.0 mg/kg	28	11.6	9	0	0	0	91	0	0	0
86D00790	F	30.0 mg/kg	28	7.9	17	0	0	0	83	0	0	0
86D00794	F	30.0 mg/kg	28	5.7	9	0	2	0	89	0	0	0
86D00821	F	30.0 mg/kg	28	5.2	8	0	0	0	92	0	0	0
86D00842	F	30.0 mg/kg	28	4.9	14	0	2	0	84	0	0	0
Mean				7.06	11.4	0.0	0.8	0.0	87.8	0.0	0.0	0.0
Std Dev				2.80	3.9	0.0	1.1	0.0	4.1	0.0	0.0	0.0
86D00775	F	60.0 mg/kg	28	8.3	11	0	1	0	88	0	0	0
86D00782	F	60.0 mg/kg	28	7.4	10	0	0	0	90	0	0	0
86D00797	F	60.0 mg/kg	28	6.7	7	0	0	0	93	0	0	0
86D00835	F	60.0 mg/kg	28	5.6	2	0	0	0	98	0	0	0
86D00841	F	60.0 mg/kg	28	5.0	11	0	1	0	88	0	0	0
Mean				6.60	8.2	0.0	0.4	0.0	91.4	0.0	0.0	0.0
Std Dev				1.33	3.8	0.0	0.5	0.0	4.2	0.0	0.0	0.0
86D00754	F	90.0 mg/kg	28	7.8	14	0	0	0	86	0	0	0
86D00757	F	90.0 mg/kg	28	10.0	10	0	0	0	90	0	0	0
86D00773	F	90.0 mg/kg	28	13.9	12	0	0	0	88	0	0	0
86D00779	F	90.0 mg/kg	28	9.5	19	0	3	0	78	1	0	0
86D00839	F	90.0 mg/kg	28	7.2	15	0	0	0	85	0	0	0
Mean				9.68	14.0	0.0	0.6	0.0	85.4	0.2	0.0	0.0
Std Dev				2.63	3.4	0.0	1.3	0.0	4.6	0.4	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00530	M	0.0 mg/kg	90	7.15	13.9	38.8	54	19.4	35.5	0.8	746
86D00539	M	0.0 mg/kg	90	7.97	14.7	41.3	52	18.4	35.3	0.6	648
86D00557	M	0.0 mg/kg	90	8.43	15.8	42.7	51	18.7	36.9	0.8	1000
86D00566	M	0.0 mg/kg	90	8.15	15.4	42.2	52	18.8	36.3	1.0	874
86D00577	M	0.0 mg/kg	90	7.87	14.6	39.8	51	18.5	36.4	1.0	1118
86D00618	M	0.0 mg/kg	90	8.00	16.0	43.8	55	19.9	36.3	0.2	862
86D00635	M	0.0 mg/kg	90	7.78	15.8	44.0	57	20.3	35.8	0.4	724
86D00688	M	0.0 mg/kg	90	8.20	15.4	42.2	51	18.8	36.4	1.4	898
86D00706	M	0.0 mg/kg	90	6.60	14.9	42.0	55	19.6	35.4	0.4	696
86D00707	M	0.0 mg/kg	90	7.86	15.6	43.6	55	19.8	35.7	1.2	864
Mean				7.801	15.21	42.04	53.3	19.22	36.00	0.78	843.0
Std Dev				0.540	0.67	1.70	2.2	0.66	0.53	0.38	144.6
86D00531	M	1.0 mg/kg	90	6.99	14.2	38.9	55	20.3	36.4	0.6	756
86D00600	M	1.0 mg/kg	90	7.81	14.9	40.4	52	19.0	36.7	0.0	902
86D00625	M	1.0 mg/kg	90	7.60	15.7	42.6	56	20.5	36.6	0.2	830
86D00628	M	1.0 mg/kg	90	6.95	14.2	38.5	55	20.2	36.5	0.2	90
86D00634	M	1.0 mg/kg	90	8.23	15.1	41.4	50	18.4	36.3	1.0	1008
86D00666	M	1.0 mg/kg	90	7.97	15.4	42.8	54	19.3	35.9	0.4	848
86D00678	M	1.0 mg/kg	90	7.59	15.0	41.2	54	19.7	36.1	0.6	1040
86D00694	M	1.0 mg/kg	90	8.23	15.8	45.1	55	19.1	34.8	0.6	758
86D00731	M	1.0 mg/kg	90	7.32	14.5	40.1	55	19.8	36.1	0.6	838
[illegible]0734	M	1.0 mg/kg	90	8.04	15.7	43.8	55	19.5	35.7	1.0	1034
Mean				7.673	15.05	41.48	54.1	19.58	36.11	0.52	810.4
Std Dev				0.470	0.61	2.11	1.8	0.65	0.56	0.33	274.3

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00511	M	10.0 mg/kg	90	7.42	14.8	39.3	53	19.9	37.5	1.4	520
86D00526	M	10.0 mg/kg	90	7.26	14.3	38.8	53	19.6	36.6	1.0	768
86D00544	M	10.0 mg/kg	90	7.17	14.2	38.0	53	19.6	37.0	1.2	701
86D00553	M	10.0 mg/kg	90	7.42	15.3	40.4	54	20.5	37.5	0.6	907
86D00581	M	10.0 mg/kg	90	7.37	14.3	39.4	53	19.4	36.2	0.8	658
86D00583	M	10.0 mg/kg	90	7.36	15.0	39.9	54	20.3	37.4	4.2	783
86D00696	M	10.0 mg/kg	90	7.09	14.0	38.0	53	19.7	36.7	0.8	758
86D00698	M	10.0 mg/kg	90	6.11	14.6	38.5	54	20.3	37.6	1.6	840
86D00717	M	10.0 mg/kg	90	7.05	14.3	38.6	55	20.1	36.7	1.0	821
86D00723	M	10.0 mg/kg	90	7.77	14.8	39.8	51	18.9	36.9	1.0	765
Mean				7.202	14.56	39.07	53.3	19.83	37.01	1.36	752.1
Std Dev				0.435	0.41	0.82	1.1	0.49	0.47	1.04	107.1
86D00612	M	30.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT
86D00626	M	30.0 mg/kg	90	7.36	14.3	38.5	52	19.4	36.9	0.0	594
86D00636	M	30.0 mg/kg	90	7.31	15.0	39.9	54	20.4	37.3	0.2	662
86D00639	M	30.0 mg/kg	90	7.49	14.6	39.5	53	19.4	36.7	1.0	614
86D00646	M	30.0 mg/kg	90	7.61	14.8	41.0	54	19.5	36.0	0.0	914
86D00655	M	30.0 mg/kg	90	7.58	14.8	40.6	54	19.5	36.4	1.6	1130
86D00675	M	30.0 mg/kg	90	7.49	15.2	40.7	54	20.3	37.2	1.2	930
86D00676	M	30.0 mg/kg	90	8.10	15.9	43.1	53	19.7	36.8	0.0	928
86D00703	M	30.0 mg/kg	90	7.93	15.5	41.7	53	19.5	36.9	0.6	1016
86D00718	M	30.0 mg/kg	90	7.60	14.9	40.8	54	19.5	36.3	0.2	964
Mean				7.608	15.00	40.64	53.4	19.69	36.72	0.53	861.3
Std Dev				0.256	0.48	1.31	0.7	0.39	0.42	0.60	190.7

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00550	M	60.0 mg/kg	90	7.02	13.4	36.0	51	19.0	36.9	0.4	858
86D00570	M	60.0 mg/kg	90	7.50	15.1	40.3	54	20.1	37.3	0.6	956
86D00617	M	60.0 mg/kg	90	7.00	14.5	38.7	55	20.5	37.0	0.3	972
86D00632	M	60.0 mg/kg	90	6.83	13.7	36.2	53	19.9	37.7	0.8	854
86D00641	M	60.0 mg/kg	90	7.83	15.3	42.3	54	19.4	35.9	0.0	978
86D00684	M	60.0 mg/kg	90	8.10	15.5	42.5	52	19.0	36.2	0.0	1018
86D00686	M	60.0 mg/kg	90	8.00	14.8	40.6	51	18.5	36.3	0.6	1022
86D00689	M	60.0 mg/kg	90	8.35	14.8	41.2	49	17.8	35.9	1.2	1072
86D00690	M	60.0 mg/kg	90	7.98	15.2	40.8	51	19.1	37.2	2.4	1060
86D00699	M	60.0 mg/kg	90	6.80	13.9	38.7	57	20.5	35.9	0.4	926
Mean				7.541	14.62	39.73	52.7	19.38	36.63	0.67	971.6
Std Dev				0.584	0.73	2.29	2.4	0.88	0.67	0.71	75.8
86D00563	M	90.0 mg/kg	90	6.86	15.2	40.6	52	19.2	37.1	0.8	904
86D00565	M	90.0 mg/kg	90	6.79	13.6	36.3	53	19.9	37.1	0.4	748
86D00568	M	90.0 mg/kg	90	7.22	14.3	38.1	53	19.7	37.3	0.8	500
86D00607	M	90.0 mg/kg	90	7.79	15.6	41.6	53	19.9	37.2	1.0	850
86D00630	M	90.0 mg/kg	90	7.83	16.4	43.9	56	20.9	37.1	0.2	846
86D00652	M	90.0 mg/kg	90	7.71	15.1	41.3	54	19.5	36.4	0.8	942
86D00659	M	90.0 mg/kg	90	7.64	15.0	41.0	54	19.6	36.5	0.6	978
86D00679	M	90.0 mg/kg	90	1.69*	3.3*	9.2*	53*	19.1*	35.4*	0.4*	1212*
86D00708	M	90.0 mg/kg	90	7.69	15.1	40.7	53	19.6	36.9	0.8	1124
86D00728	M	90.0 mg/kg	90	7.84	15.2	42.1	54	19.4	35.9	1.8	910
Mean				7.486	15.06	40.62	53.6	19.74	36.83	0.80	866.9
Std Dev				0.418	0.78	2.22	1.1	0.49	0.47	0.45	172.0

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00530	M	0.0 mg/kg	90	4.3	21	0	0	0	79	0	0	0
86D00539	M	0.0 mg/kg	90	5.4	10	0	0	0	90	0	0	0
86D00557	M	0.0 mg/kg	90	5.7	8	0	1	0	91	0	0	0
86D00566	M	0.0 mg/kg	90	7.3	12	0	1	0	87	0	0	0
86D00577	M	0.0 mg/kg	90	6.5	18	0	1	0	81	0	0	0
86D00618	M	0.0 mg/kg	90	6.3	10	0	0	0	90	0	0	0
86D00635	M	0.0 mg/kg	90	6.7	17	0	1	0	82	0	0	0
86D00688	M	0.0 mg/kg	90	5.1	17	0	0	0	83	0	0	0
86D00706	M	0.0 mg/kg	90	6.0	7	0	0	0	93	0	0	0
86D00707	M	0.0 mg/kg	90	6.7	16	0	0	0	84	0	0	0
Mean				6.00	13.6	0.0	0.4	0.0	86.0	0.0	0.0	0.0
Std Dev				0.89	4.8	0.0	0.5	0.0	4.8	0.0	0.0	0.0
86D00531	M	1.0 mg/kg	90	8.1	19	0	0	0	81	0	0	0
86D00600	M	1.0 mg/kg	90	9.0	22	0	0	0	78	0	0	0
86D00625	M	1.0 mg/kg	90	6.6	20	0	0	0	80	0	0	0
86D00628	M	1.0 mg/kg	90	7.6	40	0	0	0	60	0	0	0
86D00634	M	1.0 mg/kg	90	9.9	4	0	0	0	96	0	0	0
86D00666	M	1.0 mg/kg	90	3.4	15	0	1	0	84	0	0	0
86D00678	M	1.0 mg/kg	90	4.1	11	0	1	0	88	0	0	0
86D00694	M	1.0 mg/kg	90	3.7	9	0	0	0	91	0	0	0
86D00731	M	1.0 mg/kg	90	10.5	13	0	0	0	87	0	0	0
86D00734	M	1.0 mg/kg	90	6.2	8	0	1	0	91	0	0	0
Mean				6.91	16.1	0.0	0.3	0.0	83.6	0.0	0.0	0.0
Std Dev				2.56	10.2	0.0	0.5	0.0	10.0	0.0	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00511	M	10.0 mg/kg	90	7.4	22	0	2	0	76	0	0	0
86D00526	M	10.0 mg/kg	90	4.1	7	0	0	0	93	0	0	0
86D00544	M	10.0 mg/kg	90	4.3	22	0	1	0	77	0	0	0
86D00553	M	10.0 mg/kg	90	4.4	20	0	0	0	80	0	0	0
86D00581	M	10.0 mg/kg	90	7.3	9	0	2	0	89	0	0	0
86D00583	M	10.0 mg/kg	90	8.1	13	0	0	0	87	0	0	0
86D00696	M	10.0 mg/kg	90	7.1	13	0	1	0	86	0	0	0
86D00698	M	10.0 mg/kg	90	6.9	8	0	1	0	91	0	0	0
86D00717	M	10.0 mg/kg	90	12.5	9	0	1	0	90	0	0	0
86D00723	M	10.0 mg/kg	90	7.3	14	0	0	0	86	0	0	0
Mean				6.94	13.7	0.0	0.8	0.0	85.5	0.0	0.0	0.0
Std Dev				2.46	5.8	0.0	0.8	0.0	5.9	0.0	0.0	0.0
86D00612	M	30.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT	NT
86D00626	M	30.0 mg/kg	90	6.0	6	0	0	0	94	0	0	0
86D00636	M	30.0 mg/kg	90	5.8	12	0	0	0	88	0	0	0
86D00639	M	30.0 mg/kg	90	7.4	6	0	0	0	94	0	0	0
86D00646	M	30.0 mg/kg	90	7.0	12	0	0	0	88	0	0	0
86D00655	M	30.0 mg/kg	90	4.7	7	0	1	0	92	0	0	0
86D00675	M	30.0 mg/kg	90	5.2	9	0	0	0	91	0	0	0
86D00676	M	30.0 mg/kg	90	8.6	13	0	0	0	87	0	0	0
86D00703	M	30.0 mg/kg	90	8.0	19	0	0	0	81	0	0	0
86D00718	M	30.0 mg/kg	90	5.6	8	0	1	0	91	0	0	0
Mean				6.48	10.2	0.0	0.2	0.0	89.6	0.0	0.0	0.0
Std Dev				1.33	4.2	0.0	0.4	0.0	4.1	0.0	0.0	0.0

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00550	M	60.0 mg/kg	90	6.7	11	0	0	0	89	0	0	0
86D00570	M	60.0 mg/kg	90	8.2	12	0	1	0	86	1	0	0
86D00617	M	60.0 mg/kg	90	6.7	10	0	1	0	89	0	0	0
86D00632	M	60.0 mg/kg	90	7.8	11	0	0	0	89	0	0	0
86D00641	M	60.0 mg/kg	90	5.0	10	0	0	0	90	0	0	0
86D00684	M	60.0 mg/kg	90	6.7	5	0	0	0	95	0	0	0
86D00686	M	60.0 mg/kg	90	7.2	22	0	0	0	78	0	0	0
86D00689	M	60.0 mg/kg	90	8.3	25	0	0	0	75	0	0	0
86D00690	M	60.0 mg/kg	90	7.0	22	0	0	0	78	0	0	0
86D00699	M	60.0 mg/kg	90	9.9	9	0	1	0	90	0	0	0
Mean				7.35	13.7	0.0	0.3	0.0	85.9	0.1	0.0	0.0
Std Dev				1.30	6.7	0.0	0.5	0.0	6.6	0.3	0.0	0.0
86D00563	M	90.0 mg/kg	90	9.3	9	0	1	0	90	0	0	0
86D00565	M	90.0 mg/kg	90	6.1	17	0	0	0	83	0	0	0
86D00568	M	90.0 mg/kg	90	5.5	8	0	0	0	92	0	0	0
86D00607	M	90.0 mg/kg	90	7.6	11	0	0	0	89	0	0	0
86D00630	M	90.0 mg/kg	90	7.8	7	0	0	0	93	0	0	0
86D00652	M	90.0 mg/kg	90	9.1	12	0	0	0	88	0	0	0
86D00659	M	90.0 mg/kg	90	5.9	10	0	1	0	89	0	0	0
86D00679	M	90.0 mg/kg	90	1.3*	15*	0*	0*	0*	85*	0*	0*	0*
86D00708	M	90.0 mg/kg	90	6.6	32	0	0	0	68	0	0	0
86D00728	M	90.0 mg/kg	90	6.0	11	0	0	0	89	0	0	0
Mean				7.10	13.0	0.0	0.2	0.0	86.8	0.0	0.0	0.0
Std Dev				1.42	7.7	0.0	0.4	0.0	7.6	0.0	0.0	0.0

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00768	F	0.0 mg/kg	90	7.42	15.2	39.3	53	20.4	38.5	0.0	677
86D00772	F	0.0 mg/kg	90	7.44	15.5	40.7	55	20.7	37.8	0.2	574
86D00776	F	0.0 mg/kg	90	7.62	16.1	42.1	55	21.0	37.9	0.4	785
86D00778	F	0.0 mg/kg	90	5.54	15.7	41.4	55	20.7	37.7	0.6	810
86D00806	F	0.0 mg/kg	90	7.07	14.4	37.3	53	20.4	38.5	0.0	675
86D00810	F	0.0 mg/kg	90	7.19	14.7	38.6	54	20.3	37.7	0.0	769
86D00818	F	0.0 mg/kg	90	6.81	16.2	41.9	54	20.7	38.5	0.0	624
86D00833	F	0.0 mg/kg	90	8.05	15.8	42.3	53	19.6	37.1	0.2	797
86D00843	F	0.0 mg/kg	90	7.52	15.6	41.9	56	20.7	37.1	0.0	798
86D00849	F	0.0 mg/kg	90	7.75	15.7	41.1	53	20.1	37.9	0.2	884
Mean				7.241	15.49	40.66	54.1	20.46	37.87	0.16	739.3
Std Dev				0.693	0.57	1.70	1.1	0.40	0.52	0.21	96.8
86D00752	F	1.0 mg/kg	90	6.92	14.8	39.0	56	21.4	37.9	0.4	702
86D00755	F	1.0 mg/kg	90	7.34	15.0	40.0	54	20.4	37.2	1.4	927
86D00764	F	1.0 mg/kg	90	6.96	14.5	39.8	57	20.8	36.4	0.2	649
86D00774	F	1.0 mg/kg	90	7.54	15.4	41.5	55	20.4	36.9	0.2	692
86D00795	F	1.0 mg/kg	90	6.84	14.1	37.4	55	20.5	37.4	0.0	790
86D00804	F	1.0 mg/kg	90	1.92*	3.9*	10.8*	55*	19.8*	35.5*	0.4*	541*
86D00838	F	1.0 mg/kg	90	7.83	15.8	42.7	54	20.1	36.8	0.0	815
86D00840	F	1.0 mg/kg	90	6.44	13.9	36.0	56	21.5	38.5	0.0	686
86D00850	F	1.0 mg/kg	90	7.74	16.1	42.7	55	20.7	37.5	0.2	804
86D00855	F	1.0 mg/kg	90	7.49	15.8	41.7	56	21.0	37.6	0.2	519
Mean				7.233	15.04	40.09	55.3	20.76	37.36	0.29	731.6
Std Dev				0.467	0.79	2.33	1.0	0.47	0.63	0.44	117.4

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00749	F	10.0 mg/kg	90	6.97	14.8	39.1	56	21.2	37.7	0.0	909
86D00751	F	10.0 mg/kg	90	7.49	15.6	40.8	54	20.9	38.2	0.2	736
86D00753	F	10.0 mg/kg	90	7.09	14.5	38.3	54	20.4	37.7	0.0	833
86D00761	F	10.0 mg/kg	90	7.61	15.1	39.7	52	19.8	37.8	0.4	622
86D00784	F	10.0 mg/kg	90	3.65*	7.3*	19.5*	53*	19.7*	37.0*	0.2*	1160*
86D00802	F	10.0 mg/kg	90	2.91*	6.2*	15.9*	54*	21.0*	38.5*	0.6*	812*
86D00803	F	10.0 mg/kg	90	7.47	15.0	40.4	54	20.1	37.1	0.4	707
86D00805	F	10.0 mg/kg	90	7.31	15.5	40.6	55	21.2	38.1	0.0	588
86D00826	F	10.0 mg/kg	90	7.33	15.5	40.6	55	21.0	37.9	0.0	658
86D00827	F	10.0 mg/kg	90	7.24	14.9	39.4	54	20.6	37.6	0.0	603
Mean				7.314	15.11	39.86	54.3	20.65	37.76	0.13	707.0
Std Dev				0.213	0.39	0.89	1.2	0.52	0.34	0.18	114.7
86D00766	F	30.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT
86D00780	F	30.0 mg/kg	90	6.93	14.9	38.6	56	21.4	38.2	0.0	891
86D00787	F	30.0 mg/kg	90	7.03	15.0	38.0	54	21.2	39.1	0.0	635
86D00793	F	30.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT
86D00811	F	30.0 mg/kg	90	7.22	14.9	37.3	51	20.5	39.7	0.0	750
86D00812	F	30.0 mg/kg	90	7.64	15.8	40.7	53	20.6	38.7	0.0	683
86D00844	F	30.0 mg/kg	90	7.89	16.3	41.8	53	20.5	38.6	0.6	520
86D00848	F	30.0 mg/kg	90	6.90	14.4	37.4	54	20.8	38.3	0.4	886
86D00851	F	30.0 mg/kg	90	7.09	15.0	39.2	55	21.1	38.1	0.2	679
86D00854	F	30.0 mg/kg	90	7.72	16.4	42.8	55	21.2	38.2	0.2	713
Mean				7.303	15.34	39.48	53.9	20.91	38.61	0.18	719.6
Std Dev				0.389	0.73	2.07	1.6	0.36	0.55	0.23	124.2

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	RBC	HGB	HCT	MCV	MCH	MCHC	RET	PLT
86D00760	F	60.0 mg/kg	90	7.59	15.9	41.4	55	20.9	38.1	0.0	776
86D00762	F	60.0 mg/kg	90	6.37	15.3	39.6	54	20.7	38.4	0.2	657
86D00769	F	60.0 mg/kg	90	6.04	14.5	37.0	52	20.5	38.8	0.0	721
86D00770	F	60.0 mg/kg	90	6.84	14.1	36.2	53	20.5	38.6	0.8	46
86D00819	F	60.0 mg/kg	90	6.97	14.9	38.1	54	21.3	38.8	0.0	814
86D00820	F	60.0 mg/kg	90	7.51	15.5	40.0	53	20.5	38.4	0.4	803
86D00831	F	60.0 mg/kg	90	7.34	15.7	39.6	54	21.3	39.4	0.0	838
86D00845	F	60.0 mg/kg	90	7.26	15.3	39.8	55	20.9	38.1	0.6	984
86D00847	F	60.0 mg/kg	90	6.61	14.1	37.0	56	21.3	38.0	0.5	694
86D00856	F	60.0 mg/kg	90	7.73	16.4	42.9	55	21.1	38.0	0.0	670
Mean				7.026	15.17	39.16	54.1	20.90	38.46	0.26	700.3
Std Dev				0.559	0.77	2.10	1.2	0.34	0.45	0.31	249.4
86D00750	F	90.0 mg/kg	90	7.43	15.6	40.2	54	21.0	38.7	0.2	773
86D00783	F	90.0 mg/kg	90	7.01	14.7	38.1	54	20.9	38.3	0.0	637
86D00792	F	90.0 mg/kg	90	7.92	16.2	42.6	54	20.4	37.9	0.0	693
86D00798	F	90.0 mg/kg	90	7.00	14.4	38.9	56	20.6	37.0	0.0	710
86D00809	F	90.0 mg/kg	90	5.88	14.5	38.4	56	21.0	37.6	0.6	601
86D00813	F	90.0 mg/kg	90	3.33*	7.1*	18.4*	54*	21.1*	38.3*	0.2*	734*
86D00816	F	90.0 mg/kg	90	6.76	14.0	37.1	55	20.7	37.7	0.2	631
86D00817	F	90.0 mg/kg	90	7.83	16.0	43.6	56	20.4	36.6	0.0	951
86D00822	F	90.0 mg/kg	90	7.72	16.4	42.2	55	21.2	38.6	0.0	893
86D00830	F	90.0 mg/kg	90	7.73	16.5	43.1	56	21.3	38.1	0.4	803
Mean				7.253	15.37	40.47	55.1	20.83	37.83	0.16	743.6
Std Dev				0.662	0.97	2.45	0.9	0.33	0.70	0.22	121.3

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00768	F	0.0 mg/kg	90	2.9	14	0	0	0	86	0	0	0
86D00772	F	0.0 mg/kg	90	3.9	6	0	0	0	94	0	0	0
86D00776	F	0.0 mg/kg	90	2.1	12	0	0	0	88	0	0	0
86D00778	F	0.0 mg/kg	90	4.9	16	0	0	0	84	0	0	0
86D00806	F	0.0 mg/kg	90	3.3	15	0	1	0	84	0	0	0
86D00810	F	0.0 mg/kg	90	3.0	22	0	1	0	77	0	0	0
86D00818	F	0.0 mg/kg	90	3.1	8	0	1	0	90	1	0	0
86D00833	F	0.0 mg/kg	90	4.9	13	0	1	0	86	0	0	0
86D00843	F	0.0 mg/kg	90	7.7	7	0	0	0	92	1	0	0
86D00849	F	0.0 mg/kg	90	5.9	10	0	0	0	90	0	0	0
Mean				4.17	12.3	0.0	0.4	0.0	87.1	0.2	0.0	0.0
Std Dev				1.69	4.8	0.0	0.5	0.0	4.9	0.4	0.0	0.0
86D00752	F	1.0 mg/kg	90	5.6	15	0	0	0	85	0	0	0
86D00755	F	1.0 mg/kg	90	4.7	11	0	0	0	89	0	0	0
86D00764	F	1.0 mg/kg	90	3.9	14	0	0	0	86	0	0	0
86D00774	F	1.0 mg/kg	90	3.8	12	1	0	0	87	0	0	0
86D00795	F	1.0 mg/kg	90	7.2	9	0	2	0	89	0	0	0
86D00804	F	1.0 mg/kg	90	0.8*	10*	0*	0*	0*	90*	0*	0*	0*
86D00838	F	1.0 mg/kg	90	8.2	6	0	0	0	93	1	0	0
86D00840	F	1.0 mg/kg	90	8.1	7	0	0	0	93	0	0	0
86D00850	F	1.0 mg/kg	90	5.2	7	0	0	0	93	0	0	0
86D00855	F	1.0 mg/kg	90	5.3	10	0	1	0	89	0	0	0
Mean				5.78	10.1	0.1	0.3	0.0	89.3	0.1	0.0	0.0
Std Dev				1.68	3.2	0.3	0.7	0.0	3.1	0.3	0.0	0.0

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00749	F	10.0 mg/kg	90	6.1	2	0	1	0	97	0	0	0
86D00751	F	10.0 mg/kg	90	4.7	12	0	0	0	88	0	0	0
86D00753	F	10.0 mg/kg	90	5.7	11	0	0	0	89	0	0	0
86D00761	F	10.0 mg/kg	90	2.5	14	0	0	0	86	0	0	0
86D00784	F	10.0 mg/kg	90	0.0*	47*	0*	0*	0*	53*	0*	0*	0*
86D00802	F	10.0 mg/kg	90	4.5*	10*	0*	0*	0*	89*	1*	0*	0*
86D00803	F	10.0 mg/kg	90	6.4	7	0	1	0	92	0	0	0
86D00805	F	10.0 mg/kg	90	4.0	5	0	0	0	95	0	0	0
86D00826	F	10.0 mg/kg	90	4.6	7	0	2	0	91	0	0	0
86D00827	F	10.0 mg/kg	90	2.0	9	0	0	0	91	0	0	0
Mean				4.50	8.4	0.0	0.5	0.0	91.1	0.0	0.0	0.0
Std Dev				1.61	3.9	0.0	0.8	0.0	3.6	0.0	0.0	0.0
86D00766	F	30.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT	NT
86D00780	F	30.0 mg/kg	90	6.8	19	0	0	0	80	1	0	0
86D00787	F	30.0 mg/kg	90	3.9	11	0	0	0	89	0	0	0
86D00793	F	30.0 mg/kg	90	NT	NT	NT	NT	NT	NT	NT	NT	NT
86D00811	F	30.0 mg/kg	90	3.9	5	0	0	0	95	0	0	0
86D00812	F	30.0 mg/kg	90	6.8	5	0	1	0	94	0	0	0
86D00844	F	30.0 mg/kg	90	6.0	10	0	0	0	90	0	0	0
86D00848	F	30.0 mg/kg	90	6.3	10	0	0	0	90	0	0	0
86D00851	F	30.0 mg/kg	90	4.5	12	0	1	0	87	0	0	0
86D00854	F	30.0 mg/kg	90	7.3	3	0	0	0	97	0	0	0
Mean				5.69	9.4	0.0	0.3	0.0	90.3	0.1	0.0	0.0
Std Dev				1.38	5.1	0.0	0.5	0.0	5.3	0.4	0.0	0.0

* Insufficient sample for valid test result. Value not included in group mean.

Appendix N (cont.): HEMATOLOGY

Animal	Sex	Group	Day	WBC	SEG	BAN	EOS	BAS	LYM	MON	ATL	NRBC
86D00760	F	60.0 mg/kg	90	4.0	14	0	0	0	86	0	0	0
86D00762	F	60.0 mg/kg	90	4.4	10	0	1	0	89	0	0	0
86D00769	F	60.0 mg/kg	90	3.9	32	0	0	0	68	0	0	0
86D00770	F	60.0 mg/kg	90	5.2	20	0	1	0	79	0	0	0
86D00819	F	60.0 mg/kg	90	5.5	5	0	3	0	92	0	0	0
86D00820	F	60.0 mg/kg	90	6.5	14	0	1	0	85	0	0	0
86D00831	F	60.0 mg/kg	90	5.6	15	0	2	0	83	0	0	0
86D00845	F	60.0 mg/kg	90	6.2	9	0	1	0	90	0	0	0
86D00847	F	60.0 mg/kg	90	2.9	8	0	0	0	92	0	0	0
86D00856	F	60.0 mg/kg	90	8.3	9	0	1	0	89	1	0	0
Mean				5.25	13.6	0.0	1.0	0.0	85.3	0.1	0.0	0.0
Std Dev				1.55	7.8	0.0	0.9	0.0	7.3	0.3	0.0	0.0
86D00750	F	90.0 mg/kg	90	2.4	7	0	1	0	92	0	0	0
86D00783	F	90.0 mg/kg	90	3.7	12	0	0	0	88	0	0	0
86D00792	F	90.0 mg/kg	90	4.0	9	0	0	0	91	0	0	0
86D00798	F	90.0 mg/kg	90	4.3	13	0	0	0	87	0	0	0
86D00809	F	90.0 mg/kg	90	3.2	8	0	0	0	92	0	0	0
86D00813	F	90.0 mg/kg	90	1.5*	19*	0*	0*	0*	81*	0*	0*	0*
86D00816	F	90.0 mg/kg	90	2.6	17	0	0	0	83	0	0	0
86D00817	F	90.0 mg/kg	90	8.4	7	0	1	0	92	0	0	0
86D00822	F	90.0 mg/kg	90	6.0	13	0	1	0	86	0	0	0
86D00830	F	90.0 mg/kg	90	4.3	11	0	2	0	87	0	0	0
Mean				4.32	10.8	0.0	0.6	0.0	88.7	0.0	0.0	0.0
Std Dev				1.87	3.3	0.0	0.7	0.0	3.2	0.0	0.0	0.0

* Insufficient sample for valid test result. Value not included in group mean.